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DISEASES
of the
NERVOUS SYSTEM

A Practical Journal on Psychiatry and Neurology

Monograph Supplement

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Reports of Papers

READ AT

The Second Annual Meeting

OF

EASTERN PSYCHIATRIC RESEARCH ASSOCIATION, INC.

Held at

WALDORF ASTORIA HOTEL
NEW YORK, N. Y.

AND

KINGS PARK STATE HOSPITAL
KINGS PARK, N. Y.

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Foreword

LEO ALEXANDER, M.D., *President*

This monograph comprises the papers read at the second Annual Meeting of the Eastern Psychiatric Research Association, held October 12, 1957 at the Waldorf Astoria Hotel, New York City and the symposium and seminar on psychiatric electrotherapy technics held October 11, 1957 at Kings Park State Hospital, Kings Park, New York.

Through the year the Society held its four regular evening meetings. The evening presentations usually included a motion picture demonstration, illustrating various aspects of research or treatment, two original papers, a brief technical communication and a question for discussion by the members and guests. The following films were shown:

1. The Autonomic Nervous System.
2. Safe Neraval-Succinyl Anestho-Softened Cerebral Electrotherapy.
3. The Metabolic Insufficiency Syndrome.

The following papers were presented:

1. The Use of Neurochemical Agents in Child Schizophrenia. Sol Nichtern, M.D.
2. Sedac in General Psychiatric Practice.
3. Theoretical and Special Aspects with Sedac.
4. Treatment of Psychotic Patients with Sedac.
5. Treatment of Neurological Problems with Sedac.
6. Sedac in Certain Aspects of Mental Deficiency.
7. Intracranial Electrotherapy: Observations with the Sedac Unit.
8. Sedac in Hospital Practice of Psychiatry.
9. A Special Technical Study of Sedac Treatment.
10. The Psychopathology of the Hi-Fi Addict. Angus Bowes, M.D.
11. Tuberous Sclerosis: Clinical Pathological Presentation. G. Gold, M.D., and Donald B. Douglas, M.D.
12. Infectious Hepatitis: Experimental Passive-Active Immunity. A. M. Jacobs, M.D.
13. Ataractics in Mental Deficiency. H. Schiller, M.D.
14. Research in Mental Deficiency: The Use of Sedac. J. Spielman, M.D.
15. What the Parents of a Defective Child Ask of a Psychiatrist. Mr. Burt Hartman, President, Benevolent Soc. for Retarded Children, Inc.

There was also a hospital visit preceding one of the quarterly meetings with demonstrations by the members of the hospital staff. We had the pleasure this year of seeing the excellent work of Dr. Harold H. Berman and his staff with high frequency electrostimulation in mentally retarded children with neurologic diseases at the Willowbrook State School.

The annual meeting which is recorded in these pages was particularly interesting and stimulatin. The morning of October 11 was occupied with demonstrations of succinylcholine chloride relaxation technics for convulsive treatment. Various high dosage and low dosage methods were presented by members of the society including the Kings Park Staff under the leadership of Dr. Charles Buckman, who was host for the first day's program. The afternoon of the first day was occupied with presentation of electrosleep technics.

The morning of the second day was given to four round table discussions:

1. Function of the Anesthetist in Electroshock Therapy.
2. The Newer Psychiatric Drugs.
3. Experimental Investigations.
4. Usefulness of Non-Convulsive Techniques.

In the afternoon there was a symposium on Genetic Psychiatry consisting of four papers presented by outstanding researchers in this important and growing field. Research in this area offers new leads to the etiology including the biochemistry of mental disorder which may well be related to specific and hereditarily transmissible abnormalities of certain enzyme systems.

We are greatly indebted to Dr. Franz G. Kallmann for organizing the symposium and inviting the other participants. Dr. Kallmann himself presented his admirable and superbly analyzed data on twins.

The First Annual R. Thornton Wilson Award of $1,000.00 was awarded to Dr. I. Herbert Scheinberg of the Albert Einstein College of Medicine, New York City for his outstanding paper on "Hereditary Defects in Protein Synthesis as related to Psychiatry."

DISEASES *of the* Nervous System

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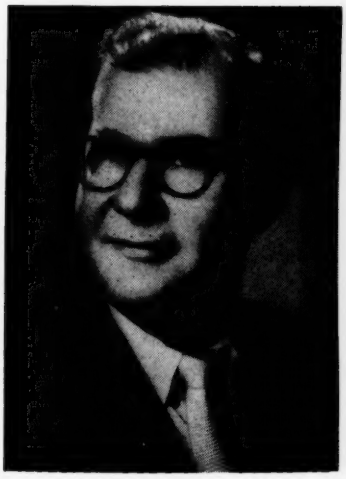

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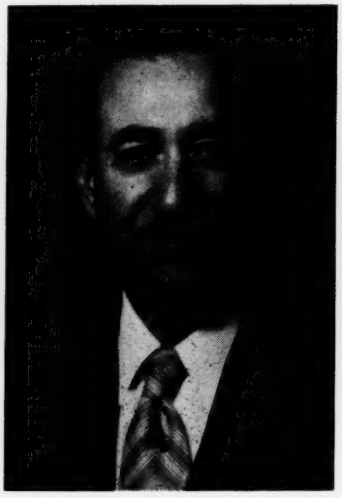

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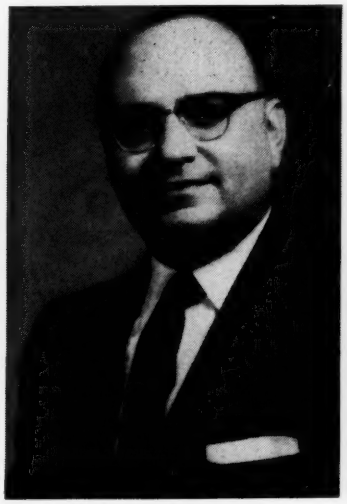

PASQUALE LOTESTA, M.D.

Progress in Genetic and Preventive Psychiatry
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An Appraisal of Psychogenetic Twin Data

FRANZ J. KALLMANN, M.D.

It is good to be back in one of the Towers of Babel of our own metropolis, and it is even more comforting to be at a meeting that is reachable by subway or Bus No. 5. Of course, there is not much yodeling on Park Avenue, and the degree of confusion prevailing in our home-grown breed of psychiatry may be almost like that observable in international settings.

However, our intra-group amenities generally tend to be less starchy than is true for the climate at global affairs. At least, one can be confused or misquoted here without benefit of earphones. In short, it is a pleasure to have been invited in this symposium to re-evaluate the merits of *psychogenetic research data,* especially those obtained in twin family investigations in relation to behavior disorders.

As information contributed by *psychogenetics* to an understanding of normal and abnormal behavior patterns is both direct and indirect, it would not be appropriate to appraise either type of evidence without reference to what Braceland[4] recently called the *science of man.* In this context, the much-misused word "psychogenetics" is employed as a condensed term embracing the whole triad of physiological, psychological and psychiatric genetics.

Although various misconceptions persist regarding the proper place of genetics in the human sciences, there now seems to be a general willingness to concede that the experimental disciplines of medical psychology and psychogenetics meet on the common ground of their concern with the variable dynamics of human behavior. The mutual interests of the two sciences lie in the very specific qualities that cause men to strive and create, to maintain health or succumb to adversity, to choose a proper mate, to work, reproduce and grow old, to die in harness or in the feeble shadows of retirement. There are biological foundations for each of these functions, and all of them are genetically controlled.[14]

While the chief objective of psychological research is to appraise quantitative and qualitative differences in traits, attitudes and personalities from an "ethnocentric" standpoint,[7] the aim of genetic studies is to search for the *basic causes.* In line with psychogenetic concepts, the changing adjustment patterns of people and societies, as well as the various modes of adaptability or non-adaptability to a multitude of technical achievements of modern man, depend on determining basic factors, all of which are powered by genic elements.

No general theory of human behavior nor causal model of specific abnormal behavior patterns can be construed in a genetic vacuum, without some reference to primary gene action. Ethnoplastic experiences which mold personality, and the formative elements which secure moldability on the human level, are end-products of the same evolutionary process, and, like both sides of a coin, defy separation into independent variables.[8,13,14]

Some of the underlying genetic principles are elementary, others highly complex. A few are still the subject of much hypothetical controversy, mainly because, as Gerard has stated, "the cleavage between natural and social science . . . is a cleavage between substance and action, body and soul, the objective and the subjective."[10] Another reason is that the science of human genetics is less than sixty years old and has been largely confined to the use of one quasi-experimental procedure—the *twin study method.*

While it is true that the complexity of human nature is such that it has prevented rapid advancement in the refinement of twin studies, this method has made it possible gradually to amass a wealth of empirical data, especially in regard to psychopathological variations. Proffering cohesion between the techniques of two coordinate scientific approaches—the psychological and the biological—the accumulated data call for certain generalizations which should condition

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the content of every psychiatric theory of fundamental intent.

Methodologically, it may be mentioned in passing that twin studies have been profitably applied in three different versions: (a) the twin-study method proper, (b) the cotwin-control method, and (c) the twin-family method. While all three versions are based on the regular occurrence of two genetically different types of twins—one-egg and two-egg—the main advantages of the third version lie in its effectiveness as a sampling method and in its inconspicuousness as a pluridisciplinary approach to total population surveys requiring combined cross-sectional and longitudinal investigations in a cooperative family setting.

The need for adequate *sampling procedures* is obvious if it is borne in mind that generalized conclusions should not be drawn from observations made in single pairs or in an unrepresentative series of pairs. The most reliable criteria for zygosity determination are dermatoglyphic and hematological data, occasionally to be supplemented by reciprocal skin grafts when the comparative scheme of the modern similarity method proves indecisive in differentiating same-sex twins.

Within the allotted time limit here, an account of psychiatrically pertinent findings, even if limited to data based on serial twin studies and rendered in telegraphic style, can only touch on a number of crucial issues. In the area of *normal personality variations,*[12,13] gene-specific derivations have been shown to range from physical, coordinative, physiognomic and temperamental characteristics to intellectual abilities, affective regulations and special talents.

In between are sex maturation patterns, variations in antibody production and neurohormonal alarm reactions, the capacity for longevity, and the ingredients for sustained tolerance of physiologic or psychologic stress—a highly essential prerequisite for a well-balanced personality. Except for one-egg twins, it is well known that each individual has his own threshold of adaptability to different types of stress, and his own pattern of stress symptom formation.

Consistent similarity in the composition of these personality components is not observed in the absence of genotypic identicalness. Two-egg twins of the same sex tend to differ as much in their personalities as any siblings reared together or apart. It is only in one-egg twins that even pronounced differences in life experiences, however adverse, are not potent enough to erase basic similarities in appearance and general personality traits.

The popular notion that the behavior patterns of one-egg twins are alike chiefly because of unusual similarity in their early environments has yet to be sustantiated. If confirmed , the argument would only strengthen rather than weaken any correctly formulated genetic theory. Psychodynamic concepts, too, are built on the premise that man is selective in respect to important aspects of his life experiences and so can be thought of as "creating his own environment."[1]

This principle is confirmed by the observation that a spiral-like development toward marked behavioral dissimilarity, such as has been reported for chronic alcoholism, delinquency or suicide, sometimes results from an apparently insignificant difference in the original adjustive patterns of one-egg twins.[13,22,23] It is axiomatic, of course, that even the finest genetic endowment can go awry, either because of an unusual combination of adverse circumstances—intrinsic or extrinsic in origin—or because of prolonged abuse. However, extreme disparities of this type are the exception rather than the rule.

In evaluating the effect of genetic factors in *psychopathological variations,* it would be generally helpful to bear in mind that, from a genetic standpoint, unusual behavior of any kind is viewed as an extremely complex and continuous chain of events in the individual's adaptive history, rather than the automatic expression of a fixed congenital error in metabolism. Accordingly, the division between a normal state of adjustment and those minor behavior deviations commonly referred to as psychoneurotic cannot be regarded as static, nor as less vaguely defined than that between normal and subnormal intelligence.

As to *psychoneurotic* reaction potentials, Eysenck and Prell[9] were among the few who availed themselves of the opportunities af-

forded by the twin-study method. In line with their findings, they classified "the neurotic personality factor" as a biological and largely gene-specific entity, estimating the genetic contribution to this "neurotic unit predisposition" as 80 per cent.

Not so specific has been Slater's[22,23] interpretation of neurotic symptoms as exaggerations of polygenically determined personality variants, less closely related to a given type of stress than to the basic personality. Despite "almost identical personality," seven of his one-egg pairs failed to present concordant psychoneurotic histories. Therefore, critical deviations in a person's history were assumed to be due to relatively chance occurrences, such as the personality of the chosen marital partner. In Slater's opinion, "one twin might suffer a mischance which would lead to a vicious circle of ill-health, social failure, hardship, discouragement and increased ill-health, while the other totally escaped." According to this theory, there are graded constitutional vulnerabilities in more than one dimension, so that "the man who breaks down with a neurotic illness is likely to be handicapped not by one constitutional weakness of severe degree, but with a number of minor weaknesses."

However, it may be noted that Shields' study[21] of same-sex pairs between the ages of 12 and 15 years provided evidence for one-egg twins being twice as likely as two-egg pairs to have the same degree of adjustive difficulty. With each child rated "on a four-point scale of psychiatric maladjustment," twins of either zygosity had no higher incidence of neurotic adjustment problems than single-born controls, but male twins and non-twins far exceeded their female counterparts in presenting some difficulty in adjustment. Only little more than one-half of the total group of school children investigated were classified as nonneurotic. Nongenetic explanations for the observed differences between one-egg and two-egg twins were rejected, somewhat summarily perhaps, especially in regard to the frequent similarities in type and severity of neurotic behavior patterns.

One of the highest one-egg concordance rates reported has been for *homosexual behavior* in the adult male,[12] although all concordant twin partners in this series denied any mutuality in overt sex relations. Nevertheless, 44 one-egg pairs yielded a nearly perfect concordance rate, with the index cases standing at least midway on the homosexuality scale applied, and with pronounced similarity in the role taken by twin partners in their individual sex activities. In the two-egg group, nearly 60 per cent of the cotwins of predominantly or exclusively homosexual index cases showed no evidence of overt homosexual behavior at any age, and only 11.5 per cent were given homosexuality ratings of five or six on Kinsey's scheme. The likeliest genetic explanation for these findings would seem to be a gene-controlled disarrangement in the balance between male and female maturation patterns, resulting in a shift toward an alternative minus variant in the integrative process of psychosexual maturation.

Another condition with a high one-egg concordance rate is an entirely different trait of more obvious organicity, namely, *convulsive disease*. The most extensive serial twin study in this area has been that of Conrad,[6] with concordance rates of 66.6 and 3.1 per cent, respectively. Unless clearly repudiated in the future, the results of this study represent strong evidence for the genetic origin of true convulsive disease.

According to Lennox and Jolly,[17] cerebral dysrhythmia is an electroencephalographic expression of the epileptic genotype, assumed to be the result of a dominant gene by the Boston group, and of polygenic factors by Alström.[3] In epileptic twins, 100 per cent of one-egg pairs and 25 per cent of two-egg pairs have been found to be equally dysrhythmic, despite marked dissimilarities in clinical symptoms.

In the area of *criminal behavior,* there is still an emphatic need for well-planned cross-sectional and longitudinal twin data. Based on the findings of Kranz, Lange and others,[15,16,22,24] criminality concordance rates vary only from 14 per cent in opposite-sex pairs to 54 and 66 per cent in same-sex two-egg and one-egg pairs, respectively. This distribution indicates that both family milieu and basic personality traits play important parts in shaping the habitual criminal. Therefore, the trend toward similar criminal behavior in two-egg pairs may stem

largely from the effect of unfavorable environmental influences.

Measured by the same yardstick, concordance in one-egg pairs can often be expected to extend to specific personality features likely to lead to a life of crime (brutality, ruthlessness, predatoriness, irresponsibility), rather than to the kind of crime perpetrated. With criminality itself determined in many cases by constellational factors, discordance may occur even in one-egg pairs, where one partner "manages to keep within the bounds of law, while the other having once taken a criminal step remains outside the law and does not find his way back."[23]

As to behavior disorders that are not sufficiently explained on a situational or experiential basis, the list of conditions for which detailed twin data are now available is headed by the *schizophrenic* and *manic-depressive* types of psychosis.[12,13] Since these two disorders do not occur interchangeably in the same twin pairs, they are assumed to be genotypically specific. The potentialities for a cyclic psychosis are probably associated with a subtle disturbance in a neurohormonal control mechanism, which ordinarily protects a person from having harmful extremes of emotional responses. The concordance rates of two-egg and one-egg twins vary from 26.3 to 95.7 per cent.

While the tendency to exceed the normal range of mood vacillation apparently requires the mutative effect of a relatively dominant gene (with a tendency to incomplete penetrance), the metabolic deficiency in a potentially schizophrenic person seems to be the result of a basically recessive unit factor. Varying clinical expressions of the disordered behavior pattern associated with the ensuing type of vulnerability to stressful experiences are probably produced by a number of modifying genes. Generally speaking, these variations depend on the type and degree of constitutional defense reactions that can be mobilized against the main biochemical (enzymatic) dysfunction. The concordance rates for two-egg and one-egg twins (based on a series of 953 pairs) are 14.5 and 86.2 per cent, respectively.

Regarding the morbidity risk for the offspring of matings between one schizophrenic and one nonschizophrenic parent, it is still correct to say that the expectancy of the disease approximates 16 per cent and depends largely on the biological qualities of the second parent. However, the question of how to designate a mode of transmission that seems distinguished by a specific unit factor for the entire syndrome, plus a number of modifying genes responsible for the variable clinical expressions of the main genotype, has become more or less a matter of semantics.

Whether the given main gene seems to be primarily dominant or recessive, or fails altogether to show simple segregation ratios, the modern concept of Mendelian heredity as recently formulated by Gordon Allen[2] implies equivalence with chromosomal heredity. At the present stage of knowledge, one no longer believes that the demonstration of a gene-specific mechanism "hinges upon the counting of simple Mendelian ratios." Hence the classifications of dominance and recessiveness are now regarded by some as no more than "operational definitions for counseling purposes."[11]

Apparently, most pathological conditions in man are neither fully dominant nor completely recessive, but only relatively so, depending upon the readiness with which the trait is detectable in the heterozygote. It has even been suggested that all carriers of mutant genes would react abnormally if put under sufficient biological stress. What can certainly be stated with assurance at this point—and has just been reemphasized by Allen[2]—is that regardless of whether the effect of a mutant gene expresses itself as an enzymatic disturbance or a lack of ability to respond to certain environmental stimuli with a normal type of behavior, the potentials of a disordered behavior pattern are likely to stem more directly from a change in primary action than can be assumed for a correlated anatomical defect.

As to the *basic metabolic deficiency* that may produce the specific potentials of a schizophrenic reaction pattern, it has been suggested that the given vulnerability component may be correlated with one of the following factors: altered reactivity to autonomic drugs, especially mecholyl; or changes in the production of a hypothetical anti-epi-

nephrine factor or of some other constituent of a faulty epinephrine metabolism, including serotonin and the oxidized adrenalin derivatives, adrenolutin and adrenochrome, which are related chemically to such substances as epinephrine, mescaline and lysergic acid; or changes in the functional properties of certain copper-containing or receptor-destroying enzymes that are essential in the control of blood plasma components, such as ceruloplasmin, or of the surface activities of red cells. One of the earliest working hypotheses assumed a genetically determined dysfunction of cellular elements, derived from the reticulo-endothelial system, and such a possibility has yet to be ruled out by adequate studies. On the whole, therefore, it must be stated with regret that despite considerable progress in the cellular, metabolic and biochemical areas of personality organization, the primary physiodynamic substrate of a schizophrenic psychosis remains veiled in mystery.

Involutional melancholia and other nonperiodic forms of depressive behavior in the involutional and senile periods have been shown by twin data to be unrelated to the manic-depressive group of disorders. There is an indirect link with the schizophrenic genotype through certain forms of emotional instability characteristic of schizoid personality traits. Other symptoms of maladjustment in the senescent period may arise either from gene-specific metabolic dysfunctions peculiar to the senium, or from graded differences in general health and survival values. Again, it is regrettable that little is known about the gene-controlled biochemical disturbance even in such well-defined clinical entities as cerebral arteriosclerosis, Huntington's chorea, and the presenile brain atrophies of the Pick or Alzheimer variety. With all these disorders, beyond demonstrating that hereditary elements play an essential part in the etiology, the ideal goal would be to show precisely how this action takes place.

Even if the search for definitive biochemical correlates of gene-specific deficiency states is not too fruitful in the immediate future, the potential value of successful progress in this direction cannot possibly be overestimated. With all available facts pointing to complex modes of causation in most psychiatric disorders, it is clear that the prospects are dim for conquering such illnesses without well-planned attacks on the cellular and molecular levels.

Reluctance to recognize the operation of genic elements in the etiology of psychoses, such as schizophrenia, is certain to have harmful consequences in a number of respects. The common denominator for damaging trends of this kind may be seen in the toleration or promotion of general attitudes that are liable to divert attention from important genetic issues.

Beyond doubt, the tendency to de-emphasize genetic factors as potential causes of behavior disorders is an occupational hazard of our profession and older than psychiatry itself as a social phenomenon. Whether accomplished by fiat or the Promethean power of allegoric expression, this tendency easily grows into a habit. While it may be obscurable by fluid levels of abstraction, it is sufficiently potent to deflect much investigative and therapeutic effort.

Aside from harmful omissions in treatment and family guidance, damage may be caused by disregard of two general genetic phenomena: (a) the hazards of a gradual increase in the number of poorly adapted carriers with a chance of reproduction, such as may result from assortative mating trends and improved medical techniques; and (b) further increases in the mutation rate of populations due to excessive use of ionizing radiation.

The theory that an increasing *load of mutations* in future generations will be the penalty for relaxing natural selection by medical advances has been supported by many genetic experts.[19,20] It is based on the estimate that the average person is heterozygous for at least eight genes of a specified variety. Under the conditions of equilibrium prevailing for present gene frequencies, there would be an effective genetic loss in the population of 20 per cent, resulting from the total of these "more or less familial patterns of weaknesses."

With a large part of this segment apt to be saved for reproduction by modern medical procedures, the frequency of mutant genes will inevitably rise to a new level. Ac-

centuated by the accumulation of gene-specific disabilities due to ionizing radiation, the adverse consequences for future generations may reach a point where the population's survival is threatened.

In view of this danger, *genetic radiation hazards* have become a matter of serious concern to everyone in recent years, including psychiatrists and neurologists and any other profession requiring extensive medical uses of X-rays. Only last year, sorely needed precautions against exposure to mutagenic energy sources were studied by special committees.[5,18] The prevailing view was that because of the cumulativeness of genetic damage caused by radiation, the average person ought not to receive more than 10 roentgens of man-made radiation up to age 30, and preferably less. The recommendations made by the committees included general public health measures designed to limit medical irradiation to safe lifetime amounts and to the lowest doses consistent with medical necessity, and the organization of much more systematic research "about all kinds and all levels of genetics."

In this kind of program, which obviously should be extended to the etiology of all psychiatric disorders of partly genetic origin, twin family studies are certain to contribute important information. Fortunately, various well-equipped laboratories are now working on these problems, and there is hope that they may soon come up with some penetrating clues.

In addition, what is needed perhaps as urgently as increased genetic knowledge is the foresight implicit in a concern with the health of future generations.[14] Real progress in this direction will depend on our present willingness to exercise such voluntary restraints as are recommended by public health authorities, and on the promise of concerted action on the part of sciences dealing with the health prospects of families and populations.

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DISCUSSION

"An Appraisal of Psychogenetic Twin Data"

JOHN D. RAINER, M.D.

In discussing Dr. Kallmann's paper, I should like to point out that his pioneering work and thought in psychogenetics is very much in the forefront of current psychiatric research. To illustrate, I would like to project into the future some of today's advanced trends and point out therein the basic character of the genetic standpoint.

Dr. Kallmann speaks of two approaches to the study of normal and disordered human behavior: the biological and psychological. To these I would like to add a third approach, a level of investigation with its own techniques, namely, the demographic or social. Indeed, these three arise from a common base: the science of human genetics.

Just as one cannot separate the continuously interacting functions of genic inheritance and environmental molding, so the demographic, psychologic and biologic frames of reference are not separate or separable. As rough indicators, however, of different predominant interests in the behavioral sciences, each in turn may be considered here as an exercise in the application of genetic knowledge to the mental sciences. The twin study method, as Dr. Kallmann indicated, runs through all of these disciplines as a made-to-order controlled experiment of nature.

Turning first to the macrocosm, we see that the application of social, epidemiological or demographic research to psychiatry is today receiving renewed attention. Aimed at relating the frequency, pattern and distribution of mental disorders to the life conditions of a given population, the main objective of such studies is to assess the differentiating effect of various outside factors on the etiology or clinical symptomatology of properly defined disease entities.[11]

Outside influences, however, react upon individuals who are also members of a population, and it is in the study of such groups that the descriptive science of demography and the biological discipline of human genetics meet. They are both concerned with the dynamics and variable stratifications of human populations. The changing composition of these groups and their various modes of interaction with physical and social surroundings depend on determining genetic principles.

Inmarriage and assortative mating patterns, formation and breakup of genetic isolates, migration, genetic drift, and the effects of mutation and selection cannot be ignored in any population study, at the risk of forming misleading opinions as to basic causes.[5] Only with the genetic base firmly established, can one assess the influence of social factors (themselves, of course, the product of evolutionary patterns). Whether a population consists of all inhabitants of an island, a province or neighborhood, or of persons sharing a severe form of deprivation such as the deaf, an epidemiological investigation of mental illness will cast light on the determinants of such illnesses, and the intricate interaction of genetic and nongenetic components, but only if it utilizes advanced techniques in both genetics and demography.

A second level of psychiatric investigation, one closely linked with our profession for several decades, is the individual, psychological or psychodynamic province. The science of psychodynamics, however, can only be considered as part of what Rado calls a unitary conceptual scheme in human biology.[10] Human consciousness, emotional and intellectual control, and adaptation are products of evolution, and both normal and extreme variations in human behavior have their genetic components. This aspect, incidentally, was always stressed by Freud, but ignored by some of his followers.

The problems of aberrant development and behavior, which are being defined with increasing clarity by psychodynamic research, can only be solved if the genetic dimension is part of the frame of reference used. With such an approach, longitudinal family studies and comparative twin studies, employing the techniques of depth psychology, may refine and extend the conclusions of the indispensable population studies in all areas of psychopathology.

If genetic findings are inseparably bound to psychodynamics, both of these categories of investigation are reflected in the next avenue of approach—that of the organization of the central and autonomic nervous systems. Mental illness, manifesting itself usually in derangements referable to this broad clinical area, is inevitably a subject for brain research. The so-called New Look in psychiatry is not so new, with Charcot, Pavlov, Kraepelin, Sherrington and the early Freud among the predecessors of modern research in the electrobiochemistry of the brain. Studies of autonomic specificity,[7] brain enzyme concentrations,[6] and conditioning and electroencephalographic patterns, modified or unmodified by drugs, have been guided fruitfully by the genetic approach, while the mechanisms of clearly defined hereditary disorders such as Huntington's chorea still await analysis.

Closely allied to the work of those focusing their attention on the central nervous system is the research dealing with the metabolism and biochemistry of the body, including endocrine function. The work of Reiss in England,[12] among others, postulates a genetically controlled variability. Of course, Dr. Kallmann points out an important proviso, namely, that a possible organic correlate of mental disorder may be the consequence, rather than the gene-specific cause, of disturbed behavior. This word of caution only makes it more essential to apply carefully the principles of scientific genetics and not be swerved one way or another by hypotheses based on old wives tales. Another reflection could be added, one offered recently by Dr. Allen in

his thoughtful statement to the 1956 Milbank conference,[1] that it should not be considered essential to find anatomical or chemical correlates for inherited behavioral characteristics, since these may have a gene-borne evolution of their own.

Finally, at the microcosmic end of the scale of research activity, there is the realm of molecular or cellular function. This is epitomized by Gerard's statement that there is no twisted thought without a twisted molecule.[2] Dr. Kallmann discussed the possible metabolic deficiencies in schizophrenia. Some of these, related to reticular-endothelial action,[8] red cell enzymatic activity,[3] susceptibility to tuberculosis, and patterns of antibody formation,[4] would suggest a widespread defect of cell units as a basic mechanism. Such a mechanism could be studied with the aid of recent findings on the relation of cell nuclei and their genic material to cytoplasmic metabolism,[13] and comparative twin investigations would be invaluable.

Thus molecular research, the province of the physical chemist,[9] merges at this basic biologic stratum with that of the pure geneticist working at the chemical, genic, chromosomal, cellular or developmental level.[13] Beyond this, our scheme could only carry us into atomic physics, and, as Dr. Kallmann has shown, even this refined discipline is not unrelated to human genetics.

In addition to its indispensable character in all branches of psychiatric research, I think the presentation you heard makes it clear that a knowledge of basic and population genetics is a necessary part of the psychiatrist's equipment in caring intelligently for his patients and their families. More than lip service must be rendered genetic factors in the proper evaluation of any psychiatric patient, hospitalized or ambulatory. The biologic orientation of the psychiatrist must have its foundation in the basic sciences, among which genetics is now a respectable member.

If today's symposium will help to eliminate the occupational hazard Dr. Kallmann refers to, and, instead, assist in furthering cooperation between psychiatrist and geneticist, each trained to understand the methods and principles of the other, this meeting may represent a milestone in psychiatry.

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Recent Developments in Behavior Genetics and Differential Psychology

JERRY HIRSCH, PH.D.

In may paper today I report on recent progress in two closely related areas of academic psychology, Behavior Genetics (BG) and Differential Psychology. BG is presently in a state of transition. Until recently active experimentation has been limited to a few laboratories. For the rest of psychology, BG represented a point of view, a program, an ambition. Now it is becoming much more active and productive. It is entering a stage in which it promises to come to grips with important problems in behavior study. Part of its impetus arises perhaps as a protest against the exclusive excellence of another starting point for the study of behavior, i.e., one that studies general processes by starting from the assumption that there is a typical or characteristic environmentally determined mode of response, which is equally well revealed by the average performance of many subjects or the performance of a single subject. BG will, no doubt, enjoy for a while at least the peculiar vigor which commonly attaches to protestantism of any sort in its early stages before it has become respectable and orthodox. The major part of its impetus, nevertheless, stems from an interest in the study of the influence of heredity on behavior. Recently I have attempted a more precise characterization of the problems and scope of BG than has as yet been offered.[3]

Whatever else it may be, BG is nothing wholly new. The behavioral aspects of its problems have long been the primary concern of psychophysics and the fields of social, abnormal, physiological and differential psychology.

BG may be defined as the science that treats of the genetic control of individual differences (ID's) in behavior. The three major features characteristic of investigations in BG involve questions of definition, estimation, and analysis.

First, it is necessary to define the behavior trait and to define the population or populations in which it is to be studied. Next, there is the estimation of the distribution of ID's throughout the defined population. Finally, there is the analysis of the genetic control of whatever behavioral differences are observed.

The definition of the behavior trait and the specification of the operations by which it is observed should provide for the reliable classification of every individual's behavior. For the definition of the population we turn to population genetics, a field whose concepts BG will find very useful. We can profitably borrow the definition of a Mendellian population: a reproductive community of individuals which share a common gene pool. This definition spells out for us the limits to be placed on our generalizations. Essentially, it warns us that the genetic structure of one population *might* be quite different from that of another and, furthermore, will remain different so long as the two populations stay reproductively isolated. To the extent that reaction patterns and ID's in reaction patterns are gene controlled and to the extent that populations differ with respect to the genes determining the reaction patterns we study, variations in behavior from one population to another may be expected.

Next, the estimation of the distribution of ID's entails sampling a population, observing the behavior of the sample and noting the distribution of individual scores over the range of behavior.

The analysis of the genetic control of ID's may proceed through several steps. One step involves estimating the heritability of a behavior. The heritability is an estimate of the proportion of the observed variance that is genetic. There are many methods for estimating heritability and all of them rest on measuring how much more closely animals

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1. As reviewed at the American Psychological Association symposium on Behavior Genetics and Differential Psychology.[3,5,6,8]

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with similar genotypes resemble each other than less closely related animals do.

A further step in genetic analysis involves specification of the nature of the genetic control of ID's. At this point we borrow techniques from experimental genetics. Genetics has advanced to where it offers us the control of an important independent variable. Enough is now known about the basic rules of the transmission of heredity from parents to offffspring so that in well studied organisms like *Drosophila* chromosomes and their parts can be juggled almost at will. In fact, the genetic consequences of this juggling are predictable with sufficient accuracy to be used routinely for doctoral dissertations in zoology. The importance for psychology of these developments in genetics is that it is now possible to manipulate genotype in much the same fashion that the psychophysicist manipulates stimuli and to observe the resulting changes in behavior as a function of genotypic differences.

The study of single behavior-traits and their genetic determination can lead to analysis of the genetic structure underlying groups of behavior-traits. Factor analysts have correlated behaviors and then disagreed widely as to both the number and nature of the factors necessary to account for their correlations. Furthermore, factors have yet to be used as experimental variables. Now that chromosomes may be manipulated as a variable it should be possible to analyze the genetic variance into components assignable to the individual chromosomes and their interactions. If the variance can be partitioned over the chromosomes for one behavior, it can be done for several behaviors. Hence, the correlations among behaviors should eventually be accounted for, at least in part, by the contributions of the chromosomes to the variances of the behaviors correlated. Thus, for example, the hoary question of G vs. s in intelligence may yet be investigated on a sound empirical basis.

Next, we consider some recent developments in BG and differential psychology. It is generally assumed by psychologists that the methods for studying ID's are almost exclusively correlational. In BG, however, both correlational and experimental methods are employed. Four types of study may be distinguished: (1) social area studies, (2) selective breeding studies, (3) family resemblance studies, and (4) experimental strain comparisons. The last category includes both the experimental analysis of the behavior of existing strains and the experimental development of strains of desired genetic constitution for behavior study.

Social area studies at present employ solely correlational methods. Observations are made on stratified populations and genetic correlations are inferred whenever behavioral correlations are greater within social strata than between social strata.

Selection studies employ both correlational and experimental methods. Genetic correlations are inferred from behavioral (and biochemical) correlations and validated experimentally by progeny tests.

Family resemblance studies also employ both methods. Behavioral correlations are inferred from genetic correlations and validated by experimental observation.

Strain comparison studies employ mainly experimental methods. Behavioral differences are inferred from genetic differences and validated by experimental observation.

Recently, working with social area correlations Professor Tryon has put forward a BG model of society.[8] He conceives of the social groups that compose society as social ecological niches. To them by social selection the varieties of human genotypes migrate, whenever possible. From them those genotypes unable to achieve adequate adaptation emigrate, if permitted, seeking other social groups congenial to their abilities and temperament. (Tryon's picture of the genetic structure of society combined with Kallmann's data on the role of heredity in pathology should lead us to look for differences among the social strata in the incidences of the various pathologies.)

According to Tryon human society is ordered by the single major variable, money-reward. Individuals receiving the same money reward but for different kinds of ability tend to gravitate to the same social area. The hierarchy of social strata is determined by the hierarchy of money-rewards characteristic of all occupations. The abilities requisite for performance in the different occupations depend upon different sensory-motor

components, which are in turn determined by different independent polygenic combinations. Most matings occur within strata so that a correlation among abilities is developed not because there is one general factor underlying achievement in all fields, but because of the selective influence of the common denominator, money-reward, which collects comparable levels of various abilities within the same social strata. In sum, Tryon argues that the general ability factor revealed by test performance is an artifact produced by the unidimensional reward system combined with an assortative mating pattern based on this reward system. The picture being drawn is a statistical one. It does not assert that *all* of the genetically controlled constitutional factors responsible for high achievement are confined to the highest social stratum or that *all* of the factors responsible for low achievement are to be found in the lowest stratum.

All factors are to be found in all strata. The strata are believed to differ, however, with respect to the relative frequency with which the factors occur.

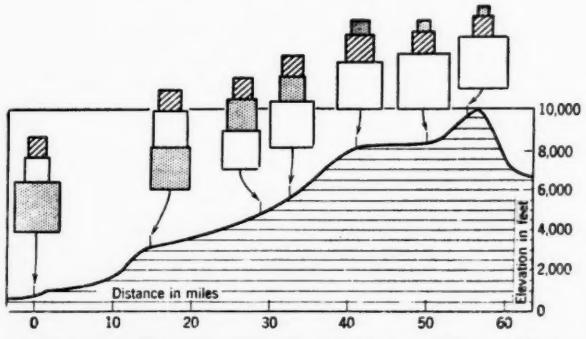

Figure 1. The relative frequencies of three different kinds of chromosomes in populations of *Drosophila pseudoobscura* living at different altitudes. (After Th. Dobzhansky, *Evolution, Genetics, and Man*, 1955, p. 148, by permission of John Wiley & Sons, Inc.)

A field study of *Drosophila* by Dobzhansky shows how genotypic balance may vary over a series of ecological niches in which all the genotypes considered are always represented[1] (p. 148). Figure 1 shows a geographic gradient or cline. The relative frequencies of three different kinds of chromosomes in populations of *Drosophila pseudoobscura* living at different elevations in the Sierra Nevada mountains of California are symbolized by the dimensions of three squares. Stippled, white, and shaded areas represent three different kinds of chromosomes. As one ascends the mountain range (moving to the right in the figure), the chromosome represented by the stippled square becomes progressively less frequent, and the chromosome represented by the white squares becomes progressively more frequent. The populations at the two altitude extremes are very different and the populations at intermediate elevations have an intermediate composition. The frequencies of genes and chromosomal variants in the gene pool change gradually.

Tryon's model of society would extend Dobzhansky's picture from three variants in one *Drosophila* chromosome pair to the almost infinite number of variants in the 24 human chromosome pairs.

About three years ago Professor Krech and his associates at Berkeley discovered that the stereotypy or flexibility of maze performance in rats is associated with the concentration of certain brain enzymes and that the level of the enzyme concentration in specific areas of the brain is genetically determined.

Animals are being selectively bred for specific brain chemistry characteristics, viz., the level of the enzyme cholinesterase (ChE), and then tested for behavioral differences. (ChE activity is considered to be an index to the metabolism of the choline acetylase-acetylcholine-cholinesterase system, and as such is a substance which is significant in normal neural functioning.) Animals that respond predominantly in terms of spatial and kinesthetic cues show higher ChE activity than do animals that respond in terms of visual brightness cues. Krech interprets his data as indicating that the "adaptiveness" of behavior is related to ChE level because the spatial or high ChE animals can be shown to vary their performance rather quickly when the cues to the solution of the problem are changed.[5] Whereas the visual or low ChE animals exhibit more stereotyped behavior, they continue responding to the formerly correct cues much longer than the high ChE animals. Thus, if ChE level proves to be related to many types of behavior, it might throw some light on the G-specificity problem in intelligence, since a chemical sys-

tem could represent a general factor in the nervous system.

We have already heard how by means of the twin study version of the family resemblance method Dr. Kallmann and his associates have gathered convincing evidence that genetic constitution plays an important role in homosexuality and in many of the behavior pathologies.

Hence, a clearcut picture is developing of the role of heredity in both normal and abnormal behavior. Our next problem on the BG agenda is to learn something about the genetic mechanisms underlying ID's in behavior. In Tryon's famous experiment demonstrating the inheritance of maze-learning ability in rats it was never possible to fathom the nature of the genetic mechanism underlying ID's in this behavior because mammalian genetics is not at a stage where detailed analysis is feasible.[7] Grüneberg, the leading authority on mouse genetics, states that "The . . . mouse is the mammal whose genetics has been most intensively studied . . ." but nevertheless "While the contributions of mouse genetics . . . are impressive . . . its . . . findings are, on the whole, confirmatory to results established long ago with quicker breeding organisms like *Drosophila*"[2] (pp. 1-2). Since *Drosophila* studies have already led the way in the fields of morphological, physiological and population genetics, I have embarked on a program of BG investigations of *Drosophila,* in the belief that the same can be true for BG.

The next three experiments to be discussed are *Drosophila* studies. The first one is not a behavior experiment. I believe, though, that it has considerable heuristic value. It demonstrates how *Drosophila* studies reveal basic genetic mechanisms.

Figure 2 shows the chromosome complements of several sexual types from an experiment by Calvin Bridges in which the mechanism of sex determination in *Drosophila* was discovered[1] (p. 262). The dot-shaped and V-shaped chromosomes are autosomes. The sex-chromosomes in each set extend downward from the centrally placed dot chromosomes. The X-chromosomes are rod-like and the Y-chromosomes are hook-shaped. Bridge's experiment demonstrated that it was the ratio of X-chromosomes to sets of autosomes in *Drosophila melanogaster* that determines sex and not the presence or absence of Y-chromosomes. When the ratio of X-chromosomes to sets of autosomes is unity, the individual is a female. When it is 0.5 the individual is a male. Ratios lower than 0.5 produce supermales and ratios higher than unity produce superfemales. Ratios intermediate between unity and 0.5 produce intersexes. The intersexes show marked fluctuations in all characters and seem to form a bimodal group with respect to the more strictly sexual characters —on the one hand a more "female-type," and, on the other, a more "male-type."

The use of this illustration is not intended to imply that human sexual aberrations follow the same pattern. The *Drosophila* studies have revealed basic mechanisms and can provide a fertile source of hypotheses to guide research on other animals. They certainly provide a much needed antidote to the overemphasis on environmental determination that has prevailed in both psychology and psychiatry.

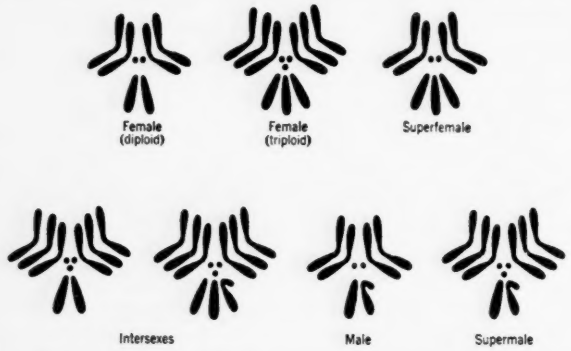

Figure 2. Chromosome complements of the different sexual types in *Drosophila melonogaster.* The X-chromosomes are rod-like, and the Y-chromosomes hook-shaped. (From Th. Dobzhansky, *Evolution, Genetics, and Man,* 1955, p. 262, by permission of John Wiley & Sons, Inc.)

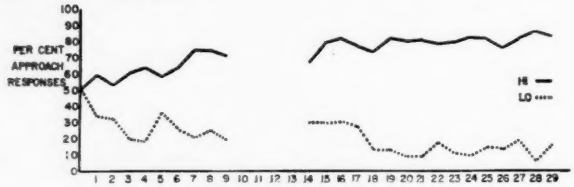

Figure 3. Response to selection for phototaxis.

Our first Drosophila behavior experiments have been in the classical tradition and we have obtained the classical results. The response to selection has been studied for two

well-known *Drosophila* behaviors, phototaxis and geotaxis. ID's have been measured with high reliability and a strong response to selection has been obtained. Figure 3 shows the Boudreau experiment[4]; the per cent approaches to light are plotted for the high and low strains over 29 generations of selection for phototaxis. Clearly there is an early response to selection and despite fluctuations the expected values of the selected strains show progressive divergence from the foundation population value of 5.16 to asymptotic values of approximately 8 for the high strain and 1.5 for the low strain. Figure 4 presents the distributions of phototactic scores for the foundation population and for filial generations 1, 2, 7, and 29. It is evident that selection effects marked changes in dispersion as well as in central tendency. These changes are reflected by the decrease in relative uncertainty over the generations shown in Figure 5.

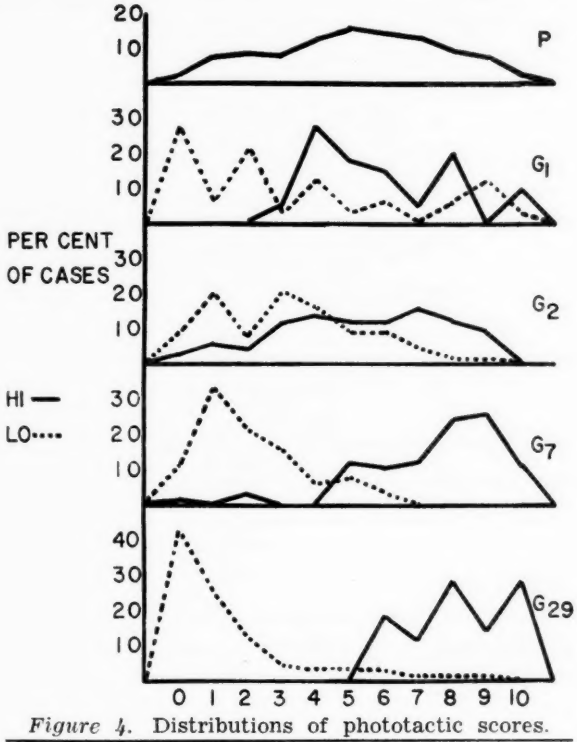

Figure 4. Distributions of phototactic scores.

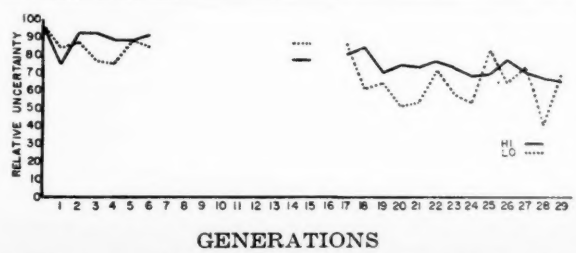

Figure 5. Changes in dispersion over 29 generations of selection.

Now we will consider an example of how *Drosophila* studies may enable us to analyze the genetics of behavior. In working with *Drosophila* the chromosome can be made the unit of analysis on the independent variable. It is in this respect that the next experiment represents a distinct departure from previous behavior experiments. In previous work, individuals have been selected for breeding on the basis of behavior scores (or biochemical trait scores) or they have been selected for behavior study on the basis of genetic correlation. Today we can assemble particular combinations of chromosomes and study the behavior of the resulting individuals.

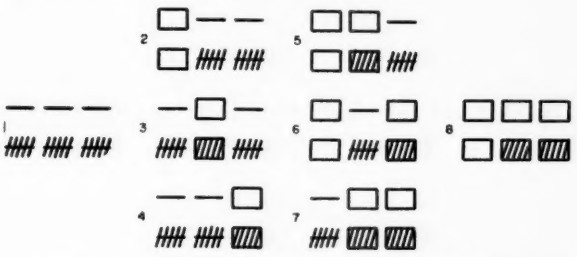

Figure 6. Chromosome complements of different experimental populations of *Drosophila melonogaster.*

Figure 6 shows the design of an experiment now being performed in our laboratories at Columbia. On the figure appear eight sets of *Drosophila* chromosome pairs. Each numbered set represents a *Drosophila* population synthesized in the laboratory expressly for the purpose of behavior study.

When a chromosome is represented by a rectangle, either cross-hatched or plain, every member of that population shares the identical chromosome. When a chromosome is represented by a line, cross-hatched or not, the genetic material on the chromosome varies randomly throughout the population. The diagrams tell us that population 1 is composed of individuals who are the least alike genetically; all chromosomes are represented by lines. The members of population 8, on the other hand, are as similar as identical twins; all chromosomes are represented by rectangles. Population 1 is a random mating population over whose genetic structure no experimental control has been exercised. The genetic structure of popu-

tem could represent a general factor in the nervous system.

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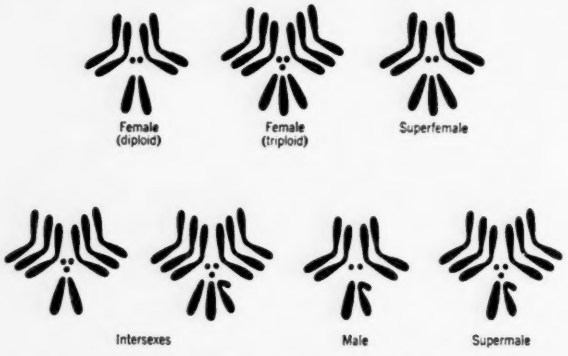

Figure 2. Chromosome complements of the different sexual types in *Drosophila melonogaster.* The X-chromosomes are rod-like, and the Y-chromosomes hook-shaped. (From Th. Dobzhansky, *Evolution, Genetics, and Man,* 1955, p. 262, by permission of John Wiley & Sons, Inc.)

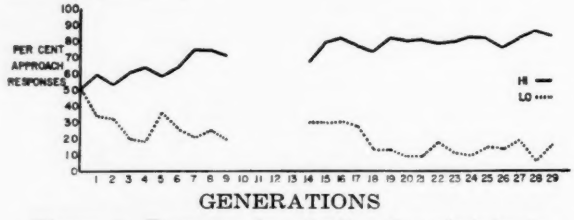

Figure 3. Response to selection for phototaxis.

Our first Drosophila behavior experiments have been in the classical tradition and we have obtained the classical results. The response to selection has been studied for two

well-known *Drosophila* behaviors, phototaxis and geotaxis. ID's have been measured with high reliability and a strong response to selection has been obtained. Figure 3 shows the Boudreau experiment[4]; the per cent approaches to light are plotted for the high and low strains over 29 generations of selection for phototaxis. Clearly there is an early response to selection and despite fluctuations the expected values of the selected strains show progressive divergence from the foundation population value of 5.16 to asymptotic values of approximately 8 for the high strain and 1.5 for the low strain. Figure 4 presents the distributions of phototactic scores for the foundation population and for filial generations 1, 2, 7, and 29. It is evident that selection effects marked changes in dispersion as well as in central tendency. These changes are reflected by the decrease in relative uncertainty over the generations shown in Figure 5.

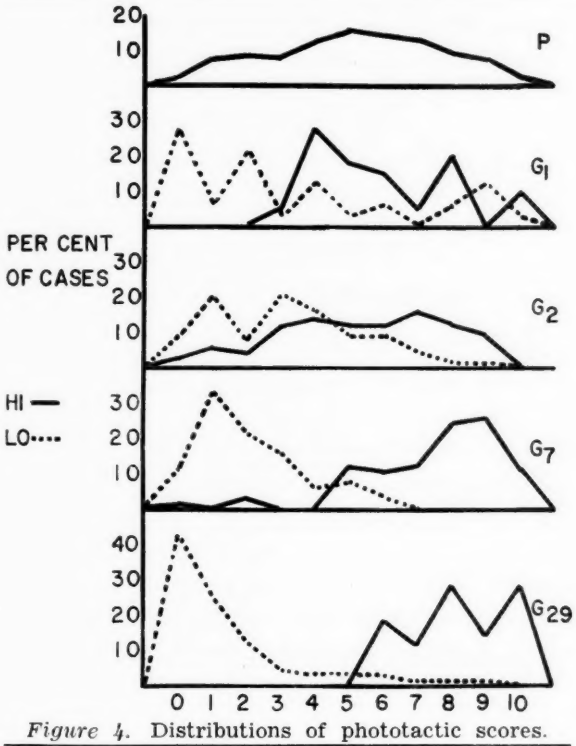

Figure 4. Distributions of phototactic scores.

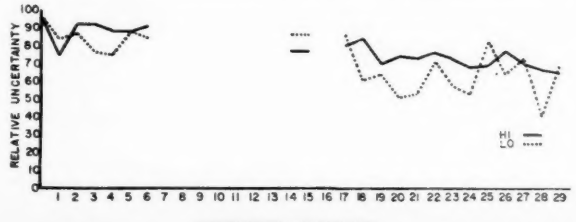

Figure 5. Changes in dispersion over 29 generations of selection.

Now we will consider an example of how *Drosophila* studies may enable us to analyze the genetics of behavior. In working with *Drosophila* the chromosome can be made the unit of analysis on the independent variable. It is in this respect that the next experiment represents a distinct departure from previous behavior experiments. In previous work, individuals have been selected for breeding on the basis of behavior scores (or biochemical trait scores) or they have been selected for behavior study on the basis of genetic correlation. Today we can assemble particular combinations of chromosomes and study the behavior of the resulting individuals.

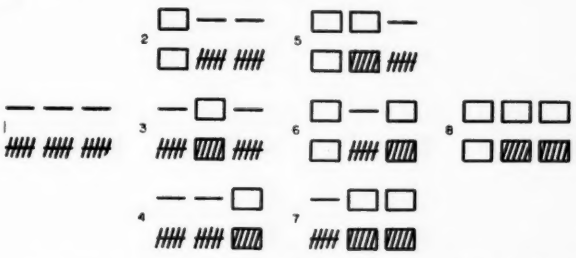

Figure 6. Chromosome complements of different experimental populations of *Drosophila melonogaster*.

Figure 6 shows the design of an experiment now being performed in our laboratories at Columbia. On the figure appear eight sets of *Drosophila* chromosome pairs. Each numbered set represents a *Drosophila* population synthesized in the laboratory expressly for the purpose of behavior study.

When a chromosome is represented by a rectangle, either cross-hatched or plain, every member of that population shares the identical chromosome. When a chromosome is represented by a line, cross-hatched or not, the genetic material on the chromosome varies randomly throughout the population. The diagrams tell us that population 1 is composed of individuals who are the least alike genetically; all chromosomes are represented by lines. The members of population 8, on the other hand, are as similar as identical twins; all chromosomes are represented by rectangles. Population 1 is a random mating population over whose genetic structure no experimental control has been exercised. The genetic structure of popu-

lation 8 has been rigorously controlled; it was synthesized in the laboratory. The degree of genetic similarity in populations 2 through 7 falls in between the two extremes represented by populations 1 and 8. In populations 2, 3, and 4 the individuals within a population are all the same with respect to the single chromosome pair represented by the pair of rectangles and are all different with respect to the other two pairs represented by the lines. In populations 5, 6, and 7 all individuals share the two pairs of chromosomes represented by the rectangles and vary randomly with respect to the single pair represented by the lines. Cross-hatching signifies merely that the two chromosomes in a pair are different, i.e., heterozygous.

The eight populations differ in known ways. Populations 2 through 7 represent all possible combinations of the chromosome pairs making up populations 1 and 8. Hence, behavioral differences observed among the eight populations can be attributed to known chromosome differences. Since these populations have been synthesized in the laboratory and can be replicated at will, it should now be possible to estimate the sampling distribution of any results obtained with them.

Experiments now in progress have been planned to incorporate all features of BG analysis. When these are completed they should afford a more complete description of the genetic control of ID's in a series of behaviors than has heretofore been possible. Our understanding need not be restricted to the chromosome level however. Whenever further analysis is desirable, genetics possesses still more refined analytic techniques available for our use.

It can readily be seen that the number of possible experiments is legion: psychologists can define an infinite number of traits and the number of genetic combinations is also unlimited. The big question facing us is which experiments to do and why.

In the area of differential psychology a fundamental methodological advance has been made by Professor McGill at Columbia.[6] He is working on the problem of analyzing general behavior processes in a context of ID's. Traditionally the study of invariant behavior processes and the study of ID's have belonged to two widely separated and practically noncommunicating academic fields. Experimental psychologists have been so deeply involved with the invariant aspects of behavior processes that they have ignored ID's almost as an item of faith. Differential psychologists, on the other hand, have been so closely identified with variant test populations that they have scarcely had time for behavior processes. The unhappy result has been that differences among individuals in vision, hearing, learning and other fundamental areas have seldom been studied.

The experimentalist's approach to ID's has been to treat them as a kind of "error" and simply wash them away by averaging data from different individuals. The difficulty with this procedure is that it often introduces distortion into the shapes of curves and hence misleads us about the form of the behavior process. Differences among individuals are seldom the same kinds of differences as differences within individuals. BG studies have amply demonstrated that they are not random differences. Carelessly averaging such differences runs the serious risk of producing an empirical result that is an artifact.

The solution to the problem is statistical and too involved for the presentation of more than a brief outline at this time. Observations are made on a behavior process in a sample of individuals. The individual curves are gathered and averaged. The statistical problem is then to determine how many different parameters are necessary to transform the group curve into the individual curves. In certain cases the number of parameters can be determined and the parameters can then be estimated. This procedure yields distributions of individual parameters, and a group curve that abstracts the relation expressed in the individual curves. McGill has done this for the general loudness function, which he has found to be a power function relating sound intensity and human loudness ratings. The behavior process in loudness judgment proves to be fairly abstract. It involves at least three individual parameters. It turns out that these purely differential properties of the loudness func-

tion are as important to an understanding of the function as is the shape of the curve.

Two things have become clear in McGill's work. One is that reconciling ID's amounts to finding an invariance of some kind existing among individuals. The second is that extreme differences among individuals make it correspondingly harder to find any invariance. Thus, we should expect that the general character of some processes would be very easy to demonstrate. Each subject's curve would superimpose itself on every other curve. At the next level of abstraction each individual's curve might be a linear transformation of each other individual's curve. More and more abstract behavior processes would require more and more complicated transformations to match individuals. It is easy to speak of a general process when individuals are related to one another by a simple transformation, but very difficult when the relations among different individuals are more complicated than the function itself. These are the extremes. Many shades of complexity exist between them.

That is the outline of McGill's solution to the problem. Invariant processes and ID's can exist together provided the differences do not become too complex. The more complex the structure of ID's, the more abstract the process and the more necessary it becomes to retreat into a psychology of individuals.

Studies are now being planned to integrate some of these developments. *Drosophila* behavior processes will be analyzed by McGill's methods and then genetic analysis can determine the nature of the genetic control, if any, of the parameters relating the individual curves to the group average.

There is a practical question that might have occurred to some of you during the presentation of these ideas. Namely, if the experimental genetics outlined in the *Drosophila* studies is supposed to represent the ideal BG study, how can there be an effective BG of animals other than *Drosophila?* After all, outside the pages of a Huxley fantasy like "Brave New World," we cannot control or synthesize the genotypes of either human beings or most other animals we study.

It is my hope that by working with *Drosophila* and using simultaneously correlational and experimental methods, we will gain sufficient understanding of the structure of genetic mechanisms underlying behavior to develop BG models, i.e., theories of the genetic control of behavior. In *Drosophila* studies, the accuracy of models developed from behavioral correlational data can be checked directly against experimentally established genetic knowledge. When our model building has become sufficiently expert at the *Drosophila* level, we might have greater confidence in it at other levels where direct genetic validation is either more difficult or at present impossible.

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DISCUSSION

"Recent Developments in Behavior Genetics and Differential Psychology"

ROBERT C. TRYON, PH.D.

Professor Hirsch has outlined the main characteristics of behavior genetics as modernly conceived. He has also described some recent developments in four main research areas of behavior genetics. I do not believe I could fruitfully add or detract from his general organization of this complex field of study. As one who has spent many years in thinking about and doing work in this field, I may offer some comments on some of his points.

As psychiatrists, your interest in behavior genetics would be, I presume, in discovering how its theories and findings may be helpful in understanding deviant behavior. May I indicate to you some ways in which it may be useful?

The selective breeding studies have usually shown that individual differences in most behaviors exist in fine degrees and not by saltatory jumps and that "high" and "low" strains are established only gradually after some generations of breeding "high x high" and "low x low." Professor Hirsch has given an example in his own selection of the two extremes of phototactic *Drosophila.* In my own experiments of some years ago on the inheritance of maze learning in rats, it took nearly a dozen generations to establish by selective breeding a strain of "maze-bright" and one of "maze-dull" animals. These results and those of other workers rather convincingly suggest that many genes, i.e., "polygenes," determine variation in most any kind of behavior. This means that the extremes—the most deviant individuals—in behavior are controlled by *multiple causes* and not by a single or a few genetic factors. Thus, in the rat experiment, a stupid rat is stupid not because he has *a* single defect somewhere but because he has many cognitive deficits, genetically determined. Extrapolating these findings to human mental deficiency, though it may be that some cases of deficiency may be traced to *a* single cause, by and large we would expect that most cases of persistent mental malfunctioning are, on the hereditary side, polygenic. I rather suspect that the hereditary bases of emotional maladjustment will turn out also to be one of great genetic complexity. If so, the role of the physician in diagnosis and treatment of extreme deviates is, as you already know, a most difficult one.

This problem of the genetic determination of the extreme deviate is only one of many problems on which behavior genetics may shed some light. I would like, in this connection, to emphasize the importance of behavior studies of *Drosophila,* such as those on which Professor Hirsch is engaged at Columbia. At first blush, you may have wondered about the psychological relevance of genetic studies of the actions of this little fruitfly. It is to be remembered that a great deal of our knowledge of the inheritance of body structures has come from work on *Drosophila* and that the *principles* of genetic control of body structures, developed out of *Drosophila* studies, have been well substantiated in other higher animals. So, likewise, we should anticipate that the principles of behavior genetics, if fully worked out on Drosophila, should have considerable generality clear across the phylogenetic scale, including man.

The only other point I would like to make is to tie together more closely the genetic conception of a population with the findings on social areas in which human beings live. As Professor Hirsch says, "The genetic structure of one population *might* be quite different from that of another . . . so long as the two populations stay reproductively isolated." Evidence has now quite definitely shown that human society, urban and suburban, is highly structured—that is, it is made up of subordinate populations concentrated in different *social* areas. Some of these subpopulations are quite isolated from each other reproductively. It is so rare for the young in a poor working-class area to marry the young in an exclusive "upper-class" area that when such a romance does occur the event is considered an important news item.

Our evidence also shows that these different "social area-populations" have great stability over long periods of time. It is true that, through social mobility, some individuals may move from one kind of social area to another. But this movement, probably on a relatively smaller scale than may be supposed, does not deny the existence of the different populations *as* populations. Much physical movement of people is probably within the same *kind* of social area. When people move from one kind to another kind, this movement may be a social sifting process, locating persons in those social ecological niches in which they fit better, genotypically.

The consequence is that the frequency of the many genes that determine cognitive capacities and emotional adaptability are probably different in these "social area-populations." We know that the people in them differ, *on the average,* in intellectual attainment as revealed by the level of their occupations and by the IQ's of their children. We know furthermore, that they differ in relative incidences of various mental diseases.

It may therefore be that psychiatry faces the complex task of dealing with different human populations in which the management of mental and emotional aberrations should proceed along different lines because the people in these populations differ genetically and culturally.

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Hereditary Defects in Protein Synthesis as Related to Psychiatry

I. HERBERT SCHEINBERG, M.D.

Inheritance of a mutant gene results in an abnormality of the primary gene product which is probably always a protein.[1] The effect of the mutation may be either to produce a quantitative deficiency or a qualitative alteration of this protein.[2] Either effect can result in disease. However, environmental factors may be so critical in determining whether the inherited defect is clinically expressed that some genetic diseases may appear to be solely environmental in origin. In this paper I shall examine the biochemical basis of several hereditary defects in protein synthesis which are associated with illnesses, and shall describe the etiologic significance of environmental factors in these illnesses. On the basis of these considerations and the recognition of the importance of hereditary factors in causing psychiatric disorders, I shall try to outline a possible experimental approach toward relating genetic defects in protein synthesis to psychiatric disease.

Let us first consider two hereditary defects in protein synthesis which are associated with illnesses which are "somatic" in almost all important respects. These two are of particular interest because they exemplify the two different kinds of effects which a mutant gene can have on the synthesis of a protein.

The first of these conditions is agammaglobulinemia. In this condition the inheritance of a sex-linked, recessive gene results in a marked, and almost complete, inability to synthesize gamma globulin antibodies.[3] A virtual absence of gamma globulins is demonstrable in the sera of these patients by electrophoresis. The important clinical result of agammaglobulinemia is an extraordinary susceptibility to repeated and severe bacterial infections: sinusitis, otitis, pneumonia, septicemia and meningitis are all common in these children. Such infections probably caused the death of all of these patients by one year of age, before the era of antibiotics.

In contrast to agammaglobulinemia, inheritance of the autosomal recessive gene which produces sickle-cell anemia does not result in a primary deficiency of hemoglobin, but in the synthesis of hemoglobin which is *qualitatively* different from normal human hemoglobin.[4] This abnormal hemoglobin, when deoxygenated, has a much lower solubility than normal hemoglobin.[5] In fact the solubility of reduced sickle-cell hemoglobin is so low that it precipitates in red-blood cells, deforming them into sickled and crescentic shapes which hemolyze easily, clog capillaries and produce infarcts.

In 1949 Pauling and his collaborators showed that there was a difference between the electrical charge on a molecule of sickle-cell hemoglobin and normal hemoglobin.[6] This difference can be detected electrophoretically. This year, with the further investigation of this disease, a "genetic milestone" has been passed in the definition, by V. M. Ingram, of the exact chemical difference between normal and sickle-cell hemoglobins.[7] For the first time the primary chemical abnormality produced by a gene, itself the result of a single mutation,[4] has been discovered! The difference between the two molecules lies in only two amino acid residues: two of the glutamic acid residues of normal hemoglobin have been replaced in sickle-cell hemoglobin by two valine residues.[8] Thus, the sickle-cell gene is responsible for the substitution of two methyl groups in sickle-cell hemoglobin for two carboxyl groups in normal hemoglobin—a change of less than 0.1 percent of the molecular weight of hemoglobin! The result is a fatal disease.

Many other diseases which are associated with hereditary defects in protein synthesis are known: hemophilia and deficiencies of other coagulation components, alcaptonuria,

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albinism and several additional hemoglobinopathies, for examples. Some of these hereditary diseases are known to be associated with disturbances in cerebral function. Two examples, in both of which gross mental deficiency occurs, are phenylpyruvic oligophrenia and galactosemia. Each of these diseases is probably characterized by quantitative deficiency of an enzyme protein rather than by a qualitatively altered form of the normal enzyme. In phenylpyruvic oligophrenia, which is inherited as an autosomal recessive trait, phenylalanine hydroxylase is the protein which is deficient and severe disturbances in the metabolism of phenylalanine result.[9] Galactosemia, probably also inherited in autosomal recessive fashion, is characterized by an almost complete deficiency of the protein phospho-galactose-uridyl transferase.[10] In the normal individual this enzyme is responsible for the conversion in the liver of galactose-1-phosphate to uridine diphosphate galactose. Since the latter compound is essential to the conversion of galactose-1-phosphate to glucose, deficiency of phospho-galactose-uridyl transferase results in an accumulation of toxic amounts of galactose-1-phosphate. This probably occurs in all tissues, although the important pathologic effects of this accumulation are seen in the kidney, lens of the eye, the liver and, of course, the brain.[11]

A third example, Wilson's disease, is associated with somewhat more subtle mental disturbances. This condition, which is also autosomal recessive in its inheritance,[12] is characterized by primary deficiency or absence of the plasma copper-protein, ceruloplasmin,[13] a blue globulin, with a molecular weight of 151,000, which contains 8 atoms of copper per molecule.[14] Although ceruloplasmin has enzymatic properties as an oxidase,[14,15] complete absence of this protein is accompanied by no detectable clinical abnormality early in life. In what way, then, is lack of ceruloplasmin associated with Wilson's disease?

Ceruloplasmin appears to regulate the absorption of dietary copper from the gastrointestinal tract.[16] It seems quite likely that *deficiency* of ceruloplasmin is accompanied by *excessive* net absorption of copper from the intestine. Consequently, an unusually large amount of copper enters the blood and thence diffuses into almost all tissues of the body. It is this copper, alone or in combination with other substances, which appears to be the agent which damages the tissues. This theory of the pathogenesis of Wilson's disease is illustrated in Fig. 1.

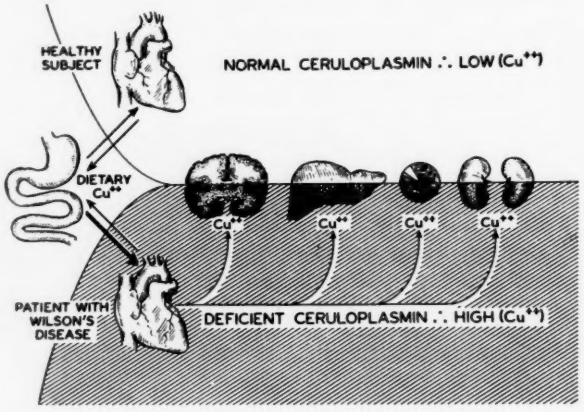

Figure 1.

The effects of the excess copper can be seen most strikingly in the eye, kidney, liver and brain.[17] In the eye, the characteristic Kayser-Fleischer ring, or crescent, apparently represents copper deposited in Descemet's membrane. In the kidney, both tubular and glomerular functions are progressively affected.[18] In the liver a severe cirrhosis or post-necrotic type of scarring develops.[19] In the brain the most obvious effects are neurological. Tremors, both at rest and on purposeful movement, incoordination, rigidity, an open-mouthed visage, drooling and slurred speech are characteristic.

More important for our discussion is the fact that patients with Wilson's disease suffer from severe emotional disturbances. One girl, now 15 years old, was for a time almost impossible for her mother to manage because of her violent temper tantrums and intense, explosive reactions to even the most casual of interpersonal relationships. Another patient, a girl of 17, functions in school and at home at a psychotic level and had, indeed, been in intensive psychiatric treatment for almost two years before the diagnosis of Wilson's disease was established. She is preoccupied with the idea that life is slipping away from her despite the fact that as yet the visceral and neurologic symptomatology of Wilson's disease is minimal,

although the diagnosis is unequivocal in the face of hepatosplenomegaly, Kayser-Fleischer rings and complete aceruloplasminemia. A third patient, a boy of 13 who has also been a behavior problem, shows intense restlessness with continual moving, repetition of ideas, and intrusion of grotesque associations into his conversation. He, too, is deeply concerned about dying, and wishes to hurry and grow up to escape death.

Now it is obvious that many, if not all, of these emotional disturbances may represent the reaction to a disabling and life-threatening disease in youthful subjects who are also subject to the severe strains of adolescence. But it is at least possible that the deposition of copper, which occurs throughout the brain, not only damages those portions concerned with motor coordination, but also injures areas which are at least partly responsible for successfully integrated and well-adapted behavior.

We now note how remarkably the phenotypic expression of each of these hereditary diseases varies with environmental factors. Agammaglobulinemia is inapparent in the absence of bacterial invasion;[3] infarction may occur in sickle-cell anemia patients if oxygen tension diminishes;[20] and the clinical manifestations of phenylketonuria,[9] galactosemia[11] and Wilson's disease can be at least partly prevented or reversed by the dietary exclusion, respectively, of phenylalanine, milk, or copper. Thus, if it were not known from genetic and biochemical investigations that these diseases are associated with hereditary protein defects they might be thought to be environmental!

Clearly, therefore, the fact that environmental factors are etiologically important in the psychoses and psychoneuroses does not imply that genetic factors are absent. This is no less true because environmental factors involving interpersonal relationships are more complex than milk or copper. There is, indeed, some direct evidence that many of these illnesses may be hereditary.[21,22] Further, we can assume that each gene which is associated with hereditary mental disease results in either a quantitative or qualitative alteration in one of the approximately 100,000 different kinds of proteins in the body,[23] in analogy with the diseases which we have already discussed. The question naturally arises, therefore, of whether these hereditary factors in psychiatric disease can be related experimentally to the defects in protein synthesis which must underlie them.

We may consider what the conditions were which permitted successful experimental investigation of the known diseases associated with hereditary defects in protein synthesis. First, recognition of the disease as a specific inherited syndrome was essential, and this could only be the result of careful clinical observation and accurate description. Second, it was necessary for at least one of the biochemical effects of the mutant gene to be demonstrable by existing experimental techniques. The first condition is self-evident, and we may see examples of the second in the diseases we have been discussing. Thus, the technique of electrophoresis made possible the demonstration of the absence of serum gamma globulins in agammaglobulinemia,[3] and the discovery of a molecular difference between sickle-cell and normal hemoglobin;[6] chromatography and the techniques of enzyme chemistry permitted precise definition of the abnormalities in metabolites and enzymes which characterize phenylketonuria[9] and galactosemia;[11] and the blue color, copper content, enzymatic activity and accessibility in plasma of ceruloplasmin made research on its relation to Wilson's disease feasible by classical methods.[13,16]

The fruitful investigation of genetic protein defects in psychiatric disease probably has similar clinical and experimental prerequisites. However, the experimental search for quantitative and qualitative differences between control subjects and psychiatrically ill patients with respect to one or several of 100,000 different proteins is formidable indeed. Yet there are three factors which may make the task feasible, and these are worth noting briefly.

First, techniques of discriminating between many similar proteins in mixtures have recently been vastly improved. For example, plasma proteins, once thought to consist almost totally of merely albumin and globulin, have been shown, by techniques of fractionation utilizing alcohols, heavy metals, and ion-exchange chromatography, as

well as by other methods, to comprise perhaps a hundred or more discrete proteins.[24,25] In particular, fractionation of serum proteins on anion-exchange cellulose can readily provide thirty different fractions each of which obviously contains more than one protein component. This type of chromatography of proteins is a tool which may be directly applicable to the problem outlined in this paper.

Second, a mutant gene which is responsible in part or completely for a psychiatric disorder may be associated with various chemical effects which are more easily investigated than the psychiatric disorder itself, and yet which may throw light on the latter. Wilson's disease, where the psychiatric disturbance may be, as we have speculated, related to the derangement in copper metabolism, is perhaps a crude example of this interaction.

Third, a mutant gene which is present in the fertilized ovum will be transferred to every cell in the body.[26] The consequence of this is sometimes extremely valuable experimentally. Although detectable effects of a gene may be present only in those cells where the primary gene product plays a physiologically significant role, occasionally other cells which may be more accessible to investigation will manifest effects of this mutant gene. Galactosemia is an example of this fact. The physiologically important site where phospho-galactose-uridyl transferase functions is the liver, but quantitatively detectable amounts of this enzyme are, in healthy subjects, present in red blood cells.[11] Thus, the protein defect in galactosemia can be demonstrated in red blood cells, and direct investigation of the liver is unnecessary. Similarly, genetically induced protein defects which affect the brain may prove to be chemically recognizable in more accessible tissues.

The finding of an association between hereditary deficiency of ceruloplasmin and Wilson's disease was no substitute for knowledge about the etiologic role of dietary copper in this illness. In fact, the only presently available effective therapy of this hereditary disease lies in modifying the environmental factors which affect the intake, absorption and excretion of copper.[27,28] By analogy it seems clear that investigation of the hereditary factors in psychiatric disease in terms of defects in protein synthesis will not be a substitute for the extensive and penetrating psychiatric and psychoanalytic research, past, present and future, which has emphasized so well the importance of environmental factors in these diseases.

New York, N. Y.

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DISCUSSION

"Hereditary Defects in Protein Synthesis As Related to Psychiatry"

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Dr. Scheinberg is to be admired for his courage in tackling so vague and unknown an area as the relation of hereditary defects in protein synthesis to the development of the syndromes encountered in psychiatry. He made quite evident the fact that the signs and symptoms pathognomonic of emotional disorders can ensue from a variety of genetically determined defects in enzyme systems. He has carefully refrained from the inference that any particular set of emotional symptoms or that any specific psychiatric syndrome may be due to some specific genetic derangement. In fact he has emphasized that it is quite possible that the same psychological aberrations may be associated with a variety of biochemical insults and may represent the subject's reaction to the presence of a disabling and life-threatening disease. Such reactions do indeed occur in patients suffering with various metabolic derangements such as diabetes mellitus, hyperthyroidism, adrenal cortical hyperplasia, etc. The fact that definite psychiatric syndromes may be associated with various endocrinopathies does not mean that the endocrinopathy is the cause of the syndrome; it just means that the endocrinopathy is reacted to by the individual just as he might react to some noxious stimulus of sufficient intensity in the external environment. The demonstration of the presence of a biochemical derangement does not preclude the influence of environmental determinants in the predisposition and precipitation of psychiatric disorders. I do not wish to imply, however, that the development of some psychiatric syndrome may not be related to some specific genetic endowment. I wish only to emphasize that the genetic endowment may act through its influence on the particular subject's responsiveness to environmental factors.

It is generally accepted that the synthesis of each protein is dependent upon the inheritance of some specific gene which serves as a template upon which amino acids are arranged in some specific orderly sequence which characterizes the particular protein. A relatively minute change in the template will induce an equivalent change in the protein that is synthesized. Thus, as Dr. Scheinberg has indicated, the hemoglobin of sickle cell anemia is related to the inheritance of a gene which is responsible for a relatively minor change in the structure of the hemoglobin. The resultant protein is "abnormal" under some environmental circumstances, "normal" under other circumstances, and even "protective" under still other circumstances as, for example, in malaria infested areas. Other examples can be cited to emphasize the fact that genetic differences do not necessarily induce physiological derangements unless specific environmental factors are brought into play. Accordingly, "normality" and "abnormality" are both genetically and environmentally determined.

Dr. Kallman's painstaking extensive studies have established that a genetic determinant is involved in the etiology of schizophrenia. At no time did he propose or even imply that the genetic factor is the sole determinant in the etiology of the psychoses. His data establish that a genetic factor is an essential but not the sole determinant in the etiology of schizophrenia. This means that the inheritance of some specific gene may result in the development of an individual who responds differently (in kind and in amount) than do others to the environmental influences that play a prepotent role in the development of the ego. In accord are the studies in progress in my laboratory which suggest that whereas the responsiveness of the hypothalamus of the non-schizophrenic population follows a normal

distribution curve, the hypothalamus of patients with schizophrenia may show no response to the particular stimuli that are being used. If this is established, all it may indicate is that the patient who develops schizophrenia is born with a hypothalamus which is less responsive to his human environment and therefore such a subject will have a different psychosexual development than one which is more responsive. Undoubtedly such a decreased responsiveness will prove to be genetically determined but that does not minimize the pathogenic influence of the psychosexual development which is dependent upon both the genetic endowment and environmental influences. It is just as fallacious to insist that a psychiatric disorder is due only to some genetically determined biochemical defect as it is to insist that such a disorder is due only to some defect in psychosexual development during the first five years of life. Both determinants are involved.

Dr. Scheinberg has indicated that both qualitative and quantitative changes in genetic endowment determine the future development of clinical derangements. The role of the quantitative factor was illustrated with the syndrome of agammaglobulinemia. Another illustration may be found in the studies which my colleagues and I have made on the etiology of duodenal ulcer. We found that the rate of gastric secretion can be expressed quantitatively in the form of a normal distribution curve, with hyposecretors at one end and hypersecretors at the other. This is true for all age groups including neonates. These and other data suggest that the rate of gastric secretion is genetically determined. It was also established that only hypersecretors develop the duodenal lesion. Such observations suggest that gastric hypersecretion is a physiological predisposing factor; they do not preclude either psychological or social determinants in the etiology of the syndrome. It is the hypersecretor who has a particular type of personality structure who develops an ulcer when exposed to a social situation which, because of his personality, is noxious to him. Essentially the physiological determinants are genetically endowed, the psychological determinants are influenced by both the genetic endowment and the early human environment while the social determinants serve as precipitating events.

Dr. Scheinberg is to be congratulated for his description of techniques which may prove useful in the uncovering of the biochemical determinants in the etiology of psychiatric disorders. Before such techniques are applied, however, we must develop an adequate taxonomy of the various psychiatric syndromes and particularly of that conglomeration usually referred to as the psychoses or "schizophrenia." The application of the proposed techniques requires the development of disciplined minds as well as disciplined hands for otherwise the future, like the past and the present, will be marked with many reports of "causes" and of "cures" which cannot be confirmed. That such disciplined minds can be developed is revealed in the presentation by Dr. Scheinberg.

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Patterns of Discovery in the Genetics of Mental Deficiency

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The advance of science has two aspects. In part it is the accumulation of factual knowledge, and in part it is the development of methods and concepts to extend this body of knowledge. Most clinicians would probably choose the first approach and content themselves with medical facts. Research workers and planners need more; they need to observe the patterns of research: long-term trends and new prospects.

It is no longer a heresy to assert the multiplicity of scientific methods.[1,2] Each branch of science evolves its own philosophy and its own patterns of discovery. Genetics combines the abstract methods of exact science with the descriptive methods of natural science, and samples research philosophies extending from that of pure mathematics to those of natural history and medical therapy. My purpose here is to examine some of the developing patterns of genetic research in the field of mental deficiency.

I. A Hierarchy of Patterns

The patterns I shall describe are of three kinds or ranks. At the highest level they embrace broad groups of disease and there are four of these patterns. At a second level, the patterns correspond to single diseases, and at the lowest level they are found in individual discoveries.

The four patterns of the first kind, or at the highest level, are important because they divide the mental deficiencies into four natural groups for research purposes. First are those diseases that give little or no evidence of genetic causation. These can be called the non-familial defects, and are illustrated by mongolism. Second, and at the opposite extreme, come the inborn errors of metabolism, like phenylpyruvic oligophrenia. These offer little challenge to the geneticist, but present straightforward physiological or biochemical problems. Third are the familial morphological syndromes. Like the metabolic errors, these usually have a simple mode of inheritance, but their pathogenesis is beyond the present horizons of biochemistry. Genetic research in this group of defects is necessarily restricted to population or epidemiologic phenomena, and is well illustrated in multiple neurofibromatosis.

A fourth research pattern on the highest level is that concerned with quantitative variation, as in height and weight. Inheritance undoubtedly has quantitative effects on the expression of all mental deficiency, but in the classic familial type quantitative factors are the central etiological problem. Here the advances of genetic research have been gradual, and more by assimilation of concepts derived from theoretical genetics than by a direct attack on mental deficiency. But this also is a pattern of discovery, and knowledge in this area may eventually be the most important contribution of genetics to public health and human betterment.

On the next lower level, within each of the four major patterns of research, one may discern as many individual patterns as there are recognized types of mental deficiency, for each disease has its own history of investigations. This history is important not only for further research in the disease concerned; the elucidation of any pathological process provides a model that is applicable, with modifications, to the investigation of other diseases.

On the lowest level, discoveries themselves have patterns, and collectively they show trends that characterize their science as a whole, in this instance biology. One such trend is the decreasing proportion of descriptions and the increasing proportion of explanations in biology. Another is the lessening dependence on chance discovery, although this will always provide crucial new leads. Finally, practical advances were once purely empirical, but today such advances are characteristically based on theoretical knowledge.[3,4] A good example of this is our increasing ability to detect healthy carriers of hereditary disease. Efforts in this direc-

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tion were suggested by Mendelian theory, and they are becoming successful mainly to the extent that they exploit the facts and theories of biochemistry.

Particular research patterns can best be illustrated in a review of progress in the four groups of mental deficiency already described.

II. Mongolism

Our first group, the non-familial diseases, are exemplified in mongolism, more appropriately called congenital acromicria by Benda.[5] Like the others of this group, it provides no easy foothold for the geneticist, but unlike them it combines a high frequency of occurrence with a relatively great degree of clinical uniformity. It was doubtless these features that led to its early recognition and to its interest for geneticists.

First distinguished by Séguin in 1846,[6] congenital acromicria was established as a syndrome 20 years later when Langdon Down[7] characterized it by comparison with the Mongolian race. By the turn of the century there were several fruitful lines of investigation and also some perplexing contradictions.[8,9,10] For example, the specific nature of mongolism seemed to indicate a single cause,[10] but support had been found for some half-dozen causes.

First suspicion in a congenital disease always falls on the prenatal environment. So, in mongolism, the first investigators looked for, and found, a high frequency of abnormal gestations. However, a large proportion of maternal complaints are in the second and third trimesters, after the anomalies of mongolism are already established,[11,12] and many of the mothers report no abnormalities. If there is any association of gestational disturbances with mongolism, it is likely that these are secondary to the essential pathology.

Other early observations were that many mongoloid children are the last in a large family, or are born to relatively old mothers. In 1909 Shuttleworth[13] succeeded in weaving all threads of evidence into one explanation. He attributed mongolism to maternal reproductive exhaustion and to all factors that might aggravate such exhaustion. Some other writers continued to disregard parity and maternal age until 1934. Then, in a thorough analysis, Penrose[14] demonstrated that both effects are beyond question. Modern studies[15] show that the maternal age effect is indeed large, giving the oldest mothers a 30-fold greater risk than the youngest ones.

The effect of maternal age excludes any complete genetic explanation, but heredity could still be a contributing influence. Early writers spoke of "neuropathic heredity" and Shuttleworth considered this one cause of early maternal exhaustion. Modern geneticists have largely abandoned as fruitless the concept of such non-specific hereditary tendencies.

Following the first report of mongolism in siblings,[16] other cases soon became known and prompted elaborate Mendelian explanations, popular at that time. The trend to reporting familial recurrence gained momentum that carried it beyond the mark. This became clear in 1953, when Øster[15] surveyed a large Danish population. Among 343 siblings born after mongoloids, he found only four more cases of mongolism. Clearly, recurrence in sibships is too rare to establish even a small role for heredity.

Reproduction by mongoloids is a still rarer event and was not well documented until 1949. Three cases have now been observed;[17,18,19] of the three babies born to mongoloid mothers, one was normal and two had acromicria. This could not be due to chance, but again the maternal age effect frustrates genetic arguments, this time by providing an alternative. We know that the physiology of 40-year-old mothers strongly disposes their babies to acromicria, and since endocrine disturbances are common in mongolism, these three mongoloid mothers may have been physiologically equivalent to 40-year-old women. No genetic explanation would then be required.

The geneticist has another strategic resource. Reports of mongolism in twins began to accumulate in 1899.[20] Beginning with Halbertsma[21] 1923, countless reviewers[22,23] found that in most pairs only one partner was affected. These all appeared to be fraternal twins. In cases where both twins were mongoloids, they were always of the same sex and usually appeared to be identical.

Many writers discount the accumulated

twin reports,[12,15] and their misgivings have perhaps been substantiated by two recent observations that depart from precedent. One pair of apparently identical twins[24] consisted of a mongoloid and a normal baby; in another case[25] the babies were of opposite sex but both mongoloid. These two cases are not crucial, however. Serious bias in the older literature is now ruled out by a report[26] on an unselected series of 32 mongoloid twins that conform to the established rules. This study also showed that the frequency of mongolism in twins is similar to that in other children, and therefore not etiologically different. The frequent concurrence of normal and mongoloid babies in the same twin pregnancy seems to rule out a complete causation by post-conceptional influences as surely as the maternal age effect rules out a complete genetic cause. Whatever may be the role of maternal physiology, the twin data indicate that relatively few embryos are capable of mongoloid development, and this susceptibility depends on their genes or their cytoplasm at the start of development.

All the lines of evidence reviewed to this point originated in the 1920's or earlier. More recently geneticists have been seeking new leads. In 1938[27] microsymptoms of mongolism were reported in close relatives of mongoloids. Attention soon focused on the hands,[28,29,30] in which parents and siblings very frequently showed acromicric tendencies. One feature found on the palms of nearly all mongoloids is known as the "distal triradius"; it occurs in about 10 per cent of normal people. Penrose[31] found a significantly increased incidence of this trait in normal relatives of mongoloids. It was especially frequent in families with two or more cases of mongolism and, most important, it appeared much more often in mothers than in fathers. Here, at last, was a definitely familial component in mongolism.

Penrose's discovery was a factual one, and its potential importance could be realized only in terms of an explanatory hypothesis. Mongolism clearly depends on a major developmental upheaval controlled somehow by the ovarian or the embryonic environment. Why should the mother's own susceptibility as an embryo, recorded in her palms, find expression later as a tendency to produce the injurious environment? This sort of puzzle cannot be solved by any logical process,[2] but such solutions are the most important kind of scientific discovery. Penrose has devised a plausible explanation that is both general enough to include many possibilities and specific enough to suggest lines of further research.

In one form Penrose's hypothesis assumes some biochemical deficiency in the early embryo. This deficiency is compensated by a supply of the unknown substance from the mother unless she also is deficient, in which case the embryo becomes mongoloid. In this form the hypothesis parallels the genetic mechanism of Rh-erythroblastosis. In contrast, however, mongolism would require a *quantitative* genetic trait, *common* to mother and embryo, and the mother's defect would be precipitated by age instead of by antigenic stimulation.

The history of mongolism should warn us against prematurely accepting or rejecting Penrose's hypothesis. The one biochemical deviation that has so far been found in congenital acromicria, excessive excretion of beta-aminoisobutyric acid,[32] does not show up significantly in the parents or siblings of mongoloids.

III. Phenylketonuria

The inborn errors of metabolism constitute our second class of mental deficiencies. These have had a wide appeal since their recognition as a group because, almost by definition, they can be reduced to chemical reactions. Phenylketonuria is perhaps the outstanding example of a disease that has been thus reduced to biochemistry and brought under medical control. Compared with mongolism, its investigation has kept to a straight and narrow path, and discoveries have followed one another in rapid succession.

The beginning of the story illustrates the fruitfulness of biochemical discovery in problems where pedigrees may be scientifically sterile. One year before Følling discovered the test for phenylketonuria, Penrose[33] published a pedigree of mental deficiency that appeared to illustrate some rare recessive hereditary disease. When Følling's test became available, Penrose[34] went back

to the family and found phenylketonuria. By itself, the pedigree would have led to nothing.

Følling's finding[35] was a good example of serendipity, that is, a chance discovery intelligently followed up. In the course of routine urine analyses, he found positive ferric chloride tests in a pair of defective siblings. He recognized their potential significance, tested 430 patients, and found six more affected families. Before publishing his discovery, he sought and found the cause of the chemical reaction, phenylpyruvic acid.

In 1937 Jervis[36] took the logical next step when he analyzed 37 families and demonstrated simple recessive inheritance. The following year Følling and associates[37] started the biochemical ball rolling with a report of high phenylalanine levels in their patients' blood. Jervis confirmed this quantitatively[38] and by 1947[39] was able to define the metabolic error. After the enzyme for this reaction had been demonstrated in normal livers,[40] Jervis[41] showed that the enzyme was absent or inactive in his patients.

The practicing physician needs explanations only as they help him to control disease. Not waiting for the enzyme studies, Woolf and Vulliamy[42] took an empirical approach along lines traditional in medicine. By 1951 technical progress had introduced synthetic diets. Phenylketonurics have too much phenylalanine, and these authors suggested a diet deficient in that amino acid. Using this principle, a number of investigators have succeeded in restoring their patients to chemical balance.[43,44,45] Whether the diet can also prevent mental retardation is not yet certain, but theory has partly caught up with practice and seems to justify optimism. It was found[40] that the crucial enzyme belongs in the liver, hence that these patients probably have the same enzymes in the brain as normal people. It appears that the gene can affect the brain only by way of the blood stream. Therefore, to the extent that the diet normalizes the blood chemistry,[46] it should prevent brain injury.

At this point the clinician would probably be content to close the books on phenylketonuria. Not so the scientists, and it is possible that the most exciting discoveries are yet to come. For example, Pauling[47] has raised the question of enzyme replacement in this disease, comparable to replacement therapy in endocrine deficiencies. Again, geneticists know that for each phenylketonuric in the population there are about 300 carriers, and it was suggested 20 years ago[34] that these carriers may be disposed to senile psychosis. Tolerance tests have become commonplace in medicine for the detection of subclinical pathology, and in 1953[48] such a test was suggested for possible carriers of the phenylketonuria gene. This has now become a reality,[49,50] and in its latest form it promises reliable identification of the heterozygous carriers. Application of this test to psychotic populations should establish or refute the alleged role of the phenylketonuria gene in senile psychoses.

IV. Multiple Neurofibromatosis

The third group of defects, the morphological familial syndromes, have not yielded biochemical leads. Genetic progress has depended on the accumulation of data, but in the collection and interpretation of these data there is play for ingenuity and even debate. In von Recklinghausen's neurofibromatosis about ten percent of patients are mentally defective, and the condition was known to recur in families from almost the earliest reports.[51] Following closely after brittle-bone disease and Huntington's chorea, it became in 1918[52] one of the first human diseases identified with dominant heredity. Doubt about this explanation lingered because of the large proportion of sporadic cases with negative family histories. But in 1933 Cockayne[53] pointed out that some of these might be new mutations, and in 1951 Borberg[54] studied a series of 79 families and found adequate agreement with irregular dominant inheritance.

A precise quantitative investigation was finally undertaken by Crowe, Schull and Neel.[55] Their monograph, published last year, illustrates the value of clinical detail and careful analysis in human population genetics. They estimated that the frequency of neurofibromatosis in Michigan was between three and four cases in every 10,000 births. Their patients had affected and normal offspring in a one-to-one ratio and all

persons known by genetic analysis to carry the gene had either skin tumors or at least six cafe-au-lait spots. The authors concluded that neurofibromatosis is a dominant disease with at least 90 percent penetrance. This justified the further assumption that nearly all sporadic cases, representing about a half of the families, were instances of new mutation. The implied rate is about one mutation in every 5000 births. The new mutations arising in each generation are compensated in the population by a 50 percent handicap in marriage and reproduction.

Clinical surveys like this can yield original and unexpected discoveries. Crowe, Schull and Neel found evidence of somatic mutation, that is, gene-mutation occurring in a somatic cell some time after the start of development, neither received nor transmitted by heredity. In four of their 137 index cases they found a circumscribed area of cutaneous pathology. The patients had no affected relatives and had produced altogether six children, all normal. These findings are consistent with somatic mutation. Attempts to verify this interpretation may shed light on neurofibromatosis and also on the general problem of somatic mutation in man.

V. Familial Mental Deficiency

The fourth major pattern of genetic investigation in mental deficiency is that concerned with quantitative variation. This kind of inheritance was understood by Galton[56] long before the rediscovery of Mendel's work, and the older school was reluctant to concede the role of Mendelian heredity in mental disorders of any kind.[57] Modern genetics has witnessed a confluence of the two streams of thought, especially in the concept of polygenes.[58] These are hypothetical genetic factors with small individual effects, expressed mainly in quantitative variation.

Galton predicted a normal or Gaussian distribution of intelligence in the population, but verification of this had to wait upon quantitative psychological methods. In the interval, Dugdale[59] described the Jukes family and Goddard,[60] after proposing the term moron, told the controversial story of the Kallikaks. Thus was defined our present concept of familial mental deficiency as a medical diagnosis. Intelligence that is much below the moron level, even if recurrent in a family, deserves a separate designation.

From the time of Goddard, at least, the genetics of familial mental defect became intimately and emotionally involved in the controversy over heredity and environment, or nature versus nurture. The Kallikak story, Goddard, and heredity itself suffered many vicissitudes of credence and acclaim that have little relation to recent progress.[61] Out of them emerged two concepts that can qualify as genetic discoveries. The first is that a family like the Kallikaks propagates its own culture as well as its own genes, and both control intelligence. Thus the cause of defect in any one child is not simply heredity.[62] Secondly, Martin Kallikak's 262 moron descendants derived only a fraction of their heredity from his poor feebleminded mistress, and the rest from other defectives, of whom some 35 were brought into the kindred as mates. The apparent multiplication of defect in succeeding generations is in part just a stepwise recruitment of similar lines from the general populace.

Goddard attributed this type of mental defect mainly to simple recessive heredity, and some early proposals for eugenics were argued on that premise. But Pearson and Jaederholm[63] showed as early as 1914 that intelligence test scores had a continuous or smooth distribution, and conformed approximately to the Gaussian or bell-shaped curve. This implies multiple small causes combining at random throughout the entire range of scores. In 1935 Roberts and co-workers[64,65] carefully plotted the low end of the scale. They found that defectives with IQ below 45 were too numerous to fit a random distribution, but that morons could be completely accommodated within the normal curve.

The etiology of familial mental deficiency is, then, different from that of low grade defect, and is to be sought in the same factors that determine normal variations in intelligence. In one sense this is discouraging. It means that the bulk of mental deficiency will probably never be explained in terms of such specific causes as phenylketonuria or maternal rubella. In another sense the implications are encouraging. As we identify and counteract influences contributing to familial mental defect, for example by improv-

ing all prenatal care, we shall favorably alter intelligence of future generations within the normal range, too. Conversely, the normal population is a favorite object of study, and whatever is learned about determination of normal intelligence will find direct application in problems of high grade mental deficiency.

The advances in the genetics of high grade mental defect have been outgrowths of theoretical discoveries and new concepts. One such concept, that heredity determines a *norm of reaction,* is an old story to geneticists[66] but has not been widely applied in discussions of mental deficiency. This was called to my attention by Diane Sank.

The nature-nurture controversy is commonly resolved with the statement that heredity sets a ceiling on a person's possible attainment, and his environment determines how much of his capacity he will use. This is misleading; consider phenylketonuria. Ten years ago a typical phenylketonuric at birth had a maximum expected IQ of about 50; this would have been regarded as his genetically fixed ceiling. Now we have discovered an environment that may give such a baby an IQ expectancy of 100 or 120, far above his alleged ceiling. As time goes on, we shall doubtless learn to improve the functioning of other defectives and of normal people, not only by medical or surgical means, but as McCulloch[67] has urged, also by educational means. As long as we hold the view that capacities are sharply limited by heredity, efforts in this direction will be restricted.

According to modern genetics, heredity determines for each quantitative trait and for each individual a (probably) bell-shaped distribution of potentialities, called a norm of reaction. Most people end up near the middle of their respective curves, but exceptional early environments can realize potentialities far above or far below a person's ordinary expectancy. The curve provided by the genes is, more precisely, a scale of probabilities. The highest probabilities, near the center of the scale, correspond to the environments most likely to be encountered. As the individual grows, prenatally and postnatally, certain possible environmental influences are eliminated and the bell-shaped curve is narrowed.

We can look at this in another way. For every person, individually, heredity fixes an IQ corresponding to each possible environment, but the choice of environments is immense and is being expanded by medical and social progress. A person whose bell-shaped curve centers at the moron level is likely to have potentialities reaching up into the normal range, and it is the future task of medicine and psychology to find the rare environments or treatments that correspond to these higher potentials.

In this last advance we see again a pattern, and one that should encourage those who deplore interdisciplinary conflicts. Both geneticists and psychologists are clarifying their concepts, and as they do so discrepancies should disappear. The view of nature-nurture interactions that is now emerging seems to eliminate one important and long-standing discrepancy.

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DISCUSSION

"Patterns of Discovery in the Genetics of Mental Deficiency"

GEORGE S. BAROFF, PH.D.

I am very pleased to have been invited to participate in this symposium and to discuss Dr. Allen's paper. I have great admiration for Dr. Allen's intellectual and scientific abilities—his ideas command respect in the forums of science.

In the early part of Dr. Allen's paper he noted that knowledge in the area of quantitative trait variation of genetic origin may eventually be one of the most important contributions of genetics to public health and human betterment. I want to underscore the importance of quantitative genetic variation. There is, after all, no reason to believe that heredity plays a lesser role in the development of normal behavior patterns than it does in the realm of psychopathology. Since most of our population deserves to be classified as "within normal limits," I unhesitatingly assert that the understanding of the hereditary mechanism underlying the phenomenon of continuous trait variation would be one of the greatest contributions of genetics.

In discussing the two mongoloid mothers who have borne mongoloid offspring, Dr. Allen observes that this is not a chance occurrence. However, he states that the maternal age effect frustrates genetic arguments by raising the possibility that the physiology of mongoloid mothers may be equivalent to that of non-mongoloid 40-year-old women. He concludes that a genetic explanation would then not be required.

It seems to the writer that the major difficulty with this conclusion is that it fails to account for the birth of a normal child to a mongoloid—nor does it indicate how a non-mongoloid mother who has borne a mongoloid is subsequently able to conceive normal children.

My point here is to illustrate that the theory of maternal physiology as *the* etiologic agent (this of course, is not what Dr. Allen maintains) raises as many questions as does the position that mongolism is primarily a genetic disorder. The questions raised by the choice of an either heredity or environment standpoint are answerable if we view mongolism as a disorder which can only arise in a genetically disposed embryo that is subjected to an adverse intrauterine environment. Both factors are necessary to the appearance of the syndrome.

I want to make a few comments regarding Dr. Allen's thought-provoking discussion of familial mental defect. My initial observation has to do with a point that is, in itself, so minor that no reference would be made were it not related to a matter of considerable significance in the area of mental retardation. In the language of Dr. Allen's paper the term moron is used in such a way as to suggest to non-specialists that it is synonymous with familial or simple or primary mental defect. In so doing, the term moron assumes a clinical as well as classificatory dimension. Clinically, the moron would be free of organic pathology sufficient to explain his retardation—and, indeed, this description fits that segment of the moron group who are classified as familial defectives. The point is that there are a group of morons who are not cases of simple mental retardation because the term in its present state of usage, or disusage, refers to an IQ range rather than to a clinical type.

In making this pedantic-like comment, I am not representing myself as a defender of the present nomenclature in this area. As a matter of fact, the term moron, imbecile and idiot are in disfavor having been supplanted by a dichotomous classification of high-grade and low-grade defect which, though more economic in that we use two terms instead of three, doesn't add particularly to our understanding of mental deficiency. The generally unsatisfactory character of the nomenclature in this realm of psychopathology results from our tendency to group a variety of conditions under one banner. This is an anathema from a research standpoint because it suggests that we know more than we do and the effect is to minimize or blot out differences between defectives. A satisfactory system of classification awaits the elucidation of the various clinical types and their etiology.

My last comment refers to Dr. Allen's elaboration of the genetic concept—norm of reaction—as it relates to hereditary traits which are continuously distributed according to the Gaussian curve. It is stated that each individual has a norm of reaction for each hereditarily determined quantitative trait and that the individual reaction norm is a probably bell-shaped distribution of potentialities relevant to this trait. It is further noted that most people function near the middle of their respective curves. From Dr. Allen's remarks with regard to the potentialities of a moron for functioning within the normal range, it appears that this bell-shaped curve (reaction norm) has the statistical properties of the normal curve. If such is the case, then Dr. Allen is raising the possibility—both disquieting and exciting—that we tend to function at about 50 per cent of our theoretical maximum. Attributing a bell-shaped curve to the reaction norm also implies that we are theoretically capable of functioning as far above our mean as below it. My impression is that the probabilities on the norm of reaction curve do not conform to a bell-shaped distribution but rather are skewed markedly to the left of our mean so that the probability of functioning below our mean is greater than the chance for surpassing it. What may sound like a strictly theoretical point is, in actuality, of considerable significance.

As a case in point—let's think of a child born to bright parents who has an IQ expectancy of 120. It is pretty well established that continuous exposure of this child to a depriving milieu may result in serious impairment of mental functioning. This child might eventually test at IQ 70 secondary to a severe and chronic personality disorder. Does this loss of 50 IQ points from his expected IQ of 120 also mean that under certain conditions he would be capable of functioning at 50 IQ units above 120, or at IQ 170, which is in the genius range? Numerically, I'm sure that there are a large number of people whose IQ's have been markedly depressed. Our orphanages used to be and our state hospitals presently are full of such individuals. On the other hand, there are so few persons at the 170 IQ level that it is obvious that under present conditions of our culture, the probability of lesser functioning is, unfortunately, greater than the probability of higher achievement. I strongly agree with Dr. Allen that the search for ways of increasing the likelihood of the realization of higher potentials is a major goal. I can see two immediate gains from such a program. Not only might this bring sanity to man but it would also introduce elegant symmetry into the curve of the norm of reaction.

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1. Function of the Anesthetist in Electroshock Therapy

IRVING E. GILBERT, M.D., SAMUEL E. WHITE, M.D., and
LEO ALEXANDER, M.D.

Why is a physician anesthesiologist employed to assist with electroshock therapy? The answer is that the specialized knowledge and technics of the anesthesiologist are essential, because potent anesthetic and relaxant drugs and procedures are employed which are potentially lethal.

The anesthesiologist is trained to maintain the vital processes in the body, including respiration and circulation with adequate oxygenation of the body tissues during the administration of chemicals and other procedures which tend to disrupt these mechanisms.

The non-anesthetist is sometimes satisfied with less than perfect oxygenation or respiration which may result in partial or complete cyanosis. As long as there is some respiration, the inexperienced may be content, but this may result in serious side effects since the cyanosis is not easily recognized. Subtle anoxemia may damage the brain, heart-muscle, kidney, or any of the special organs of the body which require nearly perfect oxygenation at all times. Occasionally non-electroshocked patients are seen who have had so-called uneventful anesthesias, but who subsequently develop memory loss, inability to concentrate or think clearly. To go a few steps further, on occasions when there is cyanosis and obvious interference with body oxygenation, the patient may become reduced to a wholly or partially decorticate state. Such patients' vegetative functions continue, while the higher cortical functions, including speech may be obliterated. While such extreme cases are rare, imperfect anesthesia with hypoxia, apart from the electroshock effects, may leave in its wake memory disturbances, and other disturbances of higher nervous activity, lasting a year or more. This imperfect anesthesia would therefore tend to compound the undesirable side effects of electroshock therapy.

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Hence, the role of the anesthesiologist is essentially to maintain oxygenation during and after such procedures. This requires specialized knowledge and training which most psychiatrists do not usually possess unless they have had adequate anesthesiologic training.

The attendance of an anesthesiologist is important not only in electroshock therapy with succinylcholine, but in any prolonged electrocoma procedures requiring specialized anesthetic administration. The psychiatrist using electroshock therapy may have sufficient physiologic knowledge to control the purely neurophysiologic aspects of the procedure, but he does not have the anesthesiologic training to secure for his patients the ideal status of oxygenation of all tissues. The co-operating anesthesiologist has the background to do just that. The anesthesiologist is capable of performing endotracheal intubation, should that be necessary, and is familiar with anesthetic technics and resuscitative procedures as well as anesthetic precautions.

The indications for the use of succinylcholine have widened to such an extent that we believe every patient receiving electroconvulsive treatment should receive thiopental and succinylcholine preparation prior to therapy. The basic indications for electroshock therapy, of course, are psychiatric. Every psychotic patient should be given the advantage of electroshock therapy unless he shows promising response to drug therapy or psychotherapy within a reasonable time, which in subacute cases may be two weeks to three months, and in acute cases two to four weeks. Suicidal, self mutilative, or homicidal tendencies make immediate ECT mandatory.

From an anesthetic viewpoint, we have felt that the only valid contraindications to ECT are acute respiratory conditions, such as pneumonia or other severe respiratory infection, which may interfere with oxygenation. We have treated uneventfully several severe asthmatics not in an acute phase.

The advantages of the technic of electroconvulsive therapy with succinylcholine under thiopental anesthesia and continued administration of oxygen under positive pressure, are manifold. Firstly, anoxia and its sequelae are avoided. In our technic the patient is kept well-oxygenated throughout the procedure. Probably as a consequence of this, there seems to be less memory disturbance. Secondly, fractures are avoided althougs lesser amounts of succinylcholine than we usually employ would be sufficient to avoid fractures. To prevent the Valsalva phenomenon, we utilize somewhat larger doses of succinylcholine. This permits the glottis to be completely relaxed and allows continued and complete inflation of the lungs, even during the convulsion. There seems to be no added risk to giving the larger doses of succinylcholine, if we are prepared to maintain the patient's respiration in the period of apnea. The larger amount of the drug seems to wear off almost as quickly as a smaller amount.

There is no strain on the body or any of its specialized systems when thiopental-succinylcholine electroshock therapy is employed, because the blood is kept completely oxygenated. Hypertensives, cardiacs, including patients after cardiac surgery, arteriosclerotics, those with previous coronary thromboses or cerebro-vascular accidents, and asthmatics have all been treated without incident.

Patients who have previously suffered fractures (usually vertebral) during electroshock therapy without the thiopental-succinylcholine regimen, have been able to continue electroshock therapy uneventfully under the thiopental-succinylcholine routine, the fractures healing during the course of treatment. Patients with herniae or with weak scars from recent abdominal surgery have also been treated successfully.

There is also a psychological advantage to this form of treatment, due to the use of thiopental. This renders the treatment less disrupting to subsequent rapport with the psychiatrist. Should the patient require treatment at a future date, there is usually no hesitation in returning for further electroshock therapy, because the previous treatment was not remembered as unpleasant.

In an out-patient or office setting, the sharing of responsibilities between psychiatrist and anesthesiologist permits a more rational utilization of the special skills of each of these members of the team. While the anesthesiologist devotes his attention to the patient in the post-treatment phase, the psychiatrist can utilize the time for the clarifying and educational psychotherapy of the relatives, a factor of outstanding importance for a sustained successful result.

In 4783 electroshock treatments under thiopental-succinylcholine modification upon 388 patients over a period of nearly 5 years there have been no fatalities or any other untoward incidents or sequelae. Patients relapsing during this period have shown little resistance or objection to further electroshock therapy.

Patients with physical infirmities including hemiplegia from recent or old cerebrovascular accidents, hypertension, cardiac insufficiency, recent and old coronary thromboses, recent surgery including recent cardiac operations, severe asthma and diabetes, have been treated successfully for their mental illnesses without aggravating or delaying recovery from these complicating physical illnesses.

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LOTHAR B. KALINOWSKY, M.D.

I consider it definitely preferable to have an anesthetist when ECT is given with succinylcholine (SCC) and thiopental. The incidence of fatalities in unpremedicated ECT, I believe, is lower than Dr. Richardson has stated. I never had one in 20 years until I began to use muscle relaxants. Although it is true that every psychiatrist can learn to oxygenate a patient, it is obvious that there are complications for which an anesthetist is better trained than a psychiatrist. At a previous discussion I mentioned the case of a patient who vomited during the convulsion, while the gag reflex was apparently abolished by the succinylcholine. This patient was saved by measures applied by the anesthetist. I may add that in unpremedicated ECT such instances never happened to me or, as far as I know, to anybody else.

I am opposed to the use of muscle relaxant drugs, but feel pushed into it for medicolegal reasons because of the possibility of fractures. Contrary to the anesthetists, I must state emphatically that I have sufficient evidence that cardiovascular patients tolerate unpremedicated ECT better than ECT with SCC and thiopental. I believe that the thiopental is more dangerous than the SCC. Yet even SCC used without Pentothal, with the unconsciousness produced by a petit mal response, is better given by an anesthetist. This does not mean that I consider it malpractice to work without an anesthetist. At the Psychiatric Institute we routinely use small amounts of SCC without an anesthetist.

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With the ever-widening use of electroconvulsive therapy in neuropsychiatric problems, especially for those in older age groups and those with serious physical disabilities, there has arisen the practice, if not the necessity, to modify the convulsive episode with a muscle relaxant or intravenous barbiturate or both. Concomitant with the use of these potent agents, the anesthesiologist has been brought into the picture.

The main functions of the anesthesiologist in electroconvulsive therapy are control of the patient's airway and provision for adequate artificial ventilation during that period when the patient is unable to ventilate himself. Healthy young individuals are able to tolerate short bouts of oxygen lack usually without difficulty but, in older patients or ones with serious physical disabilities, even short bouts may be alarming. Lack of oxygen or even decreased amounts of oxygen may, for example, cause serious cardiac arrhythmias which can lead to cardiac arrest.

At one time it was thought that cyanosis, a sign of low oxygen saturation, was necessary to insure the effectiveness of electroconvulsive therapy but this has been proved erroneous. The fact that oxygen saturation falls during unmodified electro-convulsive treatments (that is, ones in which no muscle relaxant is used) was shown several years ago by Holmberg[1] and his associates. When patients received no oxygen but were breathing room air prior to treatment, their oxygen saturation fell to dangerously low levels during treatment and remained low for several minutes after their convulsive episode terminated. However, if the patients were hyperventilated with 100% oxygen prior to the application of the electrostimulus, their oxygen saturation remained at or very near normal levels. This situation holds even truer for those treatments in which a muscle relaxant, especially succinylcholine, is used and where either a diminution or complete absence of pulmonary ventilation is achieved.

With small doses of succinylcholine (10-15 mg.) such as are used by many neuropsychiatrists, it is possible that the need for artificial ventilation with oxygen is not great in the majority of young healthy patients. But certainly in cases where larger doses are used and where older patients with a variety of diseases, particularly cardiovascular ones, are involved, the need is urgent.

Even with small doses of succinylcholine,

occasionally a patient will not begin to breathe immediately after treatment and occasionally a severe arrhythmia may occur, especially if atropine has not been given prior to treatment. In these instances an anesthesiologist or some one versed in pulmonary and cardiac resuscitation is needed.

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LOUIS PADULA, M.D.

The time has come to reappraise the methods employed in the management of the psychiatric patient treated with convulsive agents. With refinement in the use of anesthetic and relaxing agents in conjunction with electrical and chemical shock therapy, the benefit derived from the use of the improved technics may be offset by the harmful effects of the agents employed.

It may be argued that since the psychiatrist is a physician he qualified to use the anesthetic agents. Conversely, since an anesthesiologist is also a physician he should be qualified to be a psychiatrist. It must be remembered that the person best qualified to perform certain functions is the person who repeatedly performs this function and who becomes skilled in the proper indication and methods of employment of these drugs.

The anesthesiologist is trained in handling the patient in the unconscious state. By his special training in the use of anesthetic and relaxing agents and in resuscitation, he can more readily detect certain complications as soon as they arise and also because of his special training he can take immediate action to control these complications.

It cannot be said that there is any such thing as a minor or major general anesthesia. The plane of anesthesia may vary or the anesthetic time may be prolonged but the fact remains that the patient must be rendered unconscious. When one takes into consideration that many of the untoward complications in anesthesia take place during the lighter planes, it can be seen that the person administering these agents must be thoroughly skilled in their use.

It is recognized that there is a shortage of adequately trained anesthesiologists in the United States. If an anesthesiologist cannot be present, the person administering the anesthetic or relaxing agents must be fully trained and competent to treat any complication which should arise.

During the past year I have learned of five instances, following electro-convulsive therapy, where the patient vomited and aspirated varying amounts of vomitus. In three of these cases there was no anesthesiologist in attendance and in the other two an anesthesiologist was present. Unfortunately in the three cases in which no anesthesiologist was present fatalities occurred. In the other two cases the anesthesiologists were able to immediately intubate the patients and aspirate the vomitus. These patients survived.

There have been other times when the period of post-treatment apnea was so prolonged that the cardiac action of the patient became impaired. It was only the presence of a person qualified to maintain adequate oxygenation that prevented serious consequences.

Because of these cases and other similar occurrences I am led to the conclusion that an anesthesiologist should be in attendance whenever possible during electroshock therapy.

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The function of the anesthetist in electrotherapy (EST) is to assist the psychiatrist when, in the opinion of the psychiatrist, he needs such help. To say, that the anesthetist should assist in all EST's is contrary to the fact. Most EST's are given without an anesthetist.

EST came into use in 1937. From then until 1953, that is for 16 years, EST was given, except in rare instances, by the psychiatrist with only the assistance of nurses or attendants. Muscle relaxants came into use in 1940, but it was not until 1953 when succinylcholine (SCC) was introduced that the question arose concerning the need for an anesthetist to assist in the EST. Why this need should arise after 16 years is not

easily understood. There must be many reasons for it. One reason might be that by employing an anesthetist the psychiatrist shares the responsibility and burden of anxiety which the treatment arouses and thus alleviates his own feelings. Anesthetists would stress a different reason. They would say that by their aid, the patients are better treated and subjected to less risk. This may or may not be so, depending on what is understood by "treatment." If by "treatment" is meant the management of respiratory problems after the convulsions, I would say that in general, anesthetists are prepared to do this better than most psychiatrists, but by no means, all. If by "treatment" is meant the psychiatric and physical preparation and evaluation of the patient, the estimation of the doses of drugs to be given, the administration of the convulsion, the after-care, etc., I would say that the psychiatrist is better fitted to treat the patient.

We should realize and emphasize that prolonged apnea is very rarely caused by the electric current. It is usually caused by too much pretreatment medication of either or both of barbiturates and SCC. No amount of anesthetic skill can replace the careful estimation of the barbiturates and SCC dosage prior to an EST. In my opinion, most anesthetists are careless regarding the dosage of these agents which they administer to their EST patients. The anesthetists are not fearful of prolonged apneas which they regularly cause from these high dosages. They are careless, I think, for two main reasons: (1) they are confident that they can keep the patient well aereated during the period of apnea, and (2) they prefer to see a patient completely paralyzed so that not a single muscle twitches during the convulsion. The anesthetist loses sight of the fundamental fact that in EST it is unnecessary to completely paralyze the patient to obtain the desired result: that is, to prevent fractures. They are not accustomed to witnessing therapeutic convulsions which to them may be esthetically repugnant. Many psychiatrists prefer to avoid the apnea altogether by reducing pretreatment medication to the minimal dosage which will adequately soften the convulsion rather than give high doses of barbiturates and SCC and then have to treat the resulting apnea. When minimal doses of either barbiturates or SCC or both are used, prolonged apnea does not occur, and there is no need for an anesthetist to be about during the ensuing electroshock treatment.

Anesthetists have not presented us with an established statistical analysis showing that those whom they have treated have had significantly less complications than those treated by the psychiatrist alone. Until this is done, any arguments they might use in favor of the presence of the anesthetist during all EST's are not well grounded. We must remember that the mere presence of the anesthetist does not mean or guarantee that a complication will not occur. H. E. Andren and D. R. Dick,* while strongly advocating the presence of an anesthetist, report one death from cardiac rupture out of 300 patients treated. The anesthetist was not able to prevent this death. What might have prevented it would have been a careful observation of the patient between each treatment and the study of the blood pressure at the time of each treatment. The autopsy showed that the patient had died from cardiac rupture following a silent coronary attack which had occurred before the last treatment. If a sudden change in behavior had been noted, and if the blood pressure had been taken prior to this treatment and a significant drop observed and treatment withheld, this patient might have been saved. The anesthetist cannot take the place of a careful appraisal of both the physical and psychiatric status of the patient and his response to each EST. It is here, rather than in the employment of an anesthetist to treat apnea, that we will safeguard our patients.

Is the Anesthetist Ever Needed to Assist in EST?

The anesthetist is needed to assist with patients whom the psychiatrist feels are poor risks or when either because of severely impaired cardiac function, the presence of fractures, operative wounds, brittle bones,

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*Andren, H. E., and Dick, D. R.: The Therapeutic Team Approach to Modified EST. *Dis. of Nerv. Syst.*, Sept., Vol. 18, No. 10, Oct. 1957.

or other serious complications, it is desired to completely paralyze the patient during a convulsion.

It is my belief that in EST there is little need of an anesthetist but when this need is present he should at once become a partner in the EST team. If a psychiatrist feels that he needs an assistant to help him administer EST, I do not see any objection to choosing an anesthetist. Similarly, in hospital centers where many patients are treated, the presence of an anesthetist is also indicated. But I think it is not wise, as is done in some hospitals, to have the anesthetist dictate how, when, and what medication a patient should receive prior or during EST. The main function of the anesthetist in these centers would be to instruct the psychiatric residents how to properly oxygenate the patients during prolonged periods of apnea. In fact, the aim of the anesthetist should be to train all future psychiatrists in all phases of cardio-respiratory resuscitation so that eventually they will be able to take care of all their patients by themselves.

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2. Newer Psychiatric Drugs

Chlorpromazine and Dextro-Amphetamine (Dexedrine) in Psychiatric Patients

SANTINO F. LANDO, M.D.

At the Ellis Hospital, Schenectady, New York, we treated with drugs a series of ten in-patients and ten out-patients who ordinarily would require ECT. However, due to factors such as age, unusual risks, and refusal on the part of the relatives to sign permission for ECT, they were started on a combination of Dexedrine and Thorazine. The dose varied from 5 to 20 mgm of Dexedrine administered early in the day, usually in two doses, and 150 to 300 mgm of Thorazine administered in 3 to 5 doses. These cases were especially selected with particular attention to the absence of any anxiety or agitation. Psychological studies, done in all cases, occasionally revealed some anxiety developing during the course of treatment and this was offset by reducing or discontinuing the Dexedrine medication. In view of the type of cases selected, our results were considered fairly good, and there was an improvement rate of 50 to 60 percent. These cases are about to be discharged from the hospital to their families and carried on an outpatient basis. Without this medication, they all were candidates for hospitalization and certification due to the severity of their depression and withdrawal.

Many other cases have been added to the original 20, some following ECT, which was unable to hold the patient at the improved level, and accordingly, the combination of drugs was tried. The particularly encouraging results in the most recent cases have been in some of the involutional psychotic reactions and a few schizophrenics, mostly younger catatonics. A combination medication including 2½ mgm of Dexedrine and 10 mgm of Thorazine, plus a larger dosage of 5 mgm of Dexedrine and 25 mgm of Thorazine, plus a larger dosage of 5 mgm of Dexedrine and 25 mgm of Thorazine is now being manufactured. Our usual dosage presently consists of one of these combinations, either Thoradex No. 1 or Thoradex No. 2, morning and noon, supplemented with Thorazine 25 or 50 mgm in the evening and at bedtime.

Iproniazid in Depression

WILLIAM FURST, M.D.
West Orange, N. J.

I should like to comment on the use of iproniazid (marsilid) in approximately 100 cases observed by my associates and myself since January 1957. It is our impression that it is one of the most useful drugs for endogenous depression introduced in the last several decades. We have tried to restrict our case material to a diagnostic entity characterized by anhedonia, anorexia, insomnia, depression, psychomotor retardation, loss of weight, and a gradual diminution of the depression toward the end of the day. Our tentative conclusions are that roughly 3 out of 4 such cases respond as well, if not better, within a period of four to six weeks, than with electroshock therapy. Response is sometimes so dramatic that one suspects a spontaneous remission. This sometimes occurs within a period of ten to twenty days. In general, however, a continuation of the drug for three to four weeks is imperative. Our dosage scale has been 50 mgm t.i.d. for five to ten days, depending upon body weight, with reduction to 25 mgm t.i.d. for one to three weeks. This is followed by 10 mgm doses t.i.d. for two to four weeks with gradual reduction to 10 mgm once a day.

We have observed 2 cases of jaundice, one mild and one relatively severe. Probably the most disturbing and most frequent side effect is the hypotension with dizziness that develops rather quickly. Reduction of the dose or cessation of the drug completely may be necessary in highly susceptible people. One must keep in mind cerebral insufficiency in elderly people that may result from a marked reduction of blood pressure. One of our cases developed a blood pressure drop from 160/100 to 100/70 with syncope and a facial laceration in falling.

Occasionally a rapid induction of a hypomanic state will be seen. Obviously cessation of the drug is then imperative. Constipation is present in approximately 80% of

patients on this drug. As the drug dosage is reduced, the constipation is lessened. Some of our patients have complained of loss of libido and potentia while on the drug, which disappears on cessation. An interesting observation is that while many have a continuing sleep disturbance, they do not seem disturbed by their insomnia. Occasionally we have added 10 mgm doses of Ritalin twice daily to the dose of Marsilid. Dexedrine, in similar dosage, seems to potentiate the marsilid effect. One witnesses not infrequently a rather dramatic mobilization of energy stores, which promotes activity in the patients usually apathetic and withdrawn. The following are brief descriptions of several interesting responses.

1) Mrs. S.W., age 62, had previously received a total of 40 electroshock treatments, because of four cycles of severe depression. At no time did she respond completely to the treatments. Her recovery, while initiated by the electroshock treatment, did not take place until three to six months after its termination. In her last series of treatments she was insufficiently sedated and claimed that she felt "sparks on her head." For this reason she was adamant in refusing further electrotherapy. I placed her on marsilid, with some trepidation, as is usual in initiating treatment with a new drug. Within 12 days she made a dramatic remission from what was a severe depressive phase of a manic depressive psychosis. There were no side effects noted other than a drop in her blood pressure from 180/110 to 140/80. She has maintained an excellent remission during follow-up evaluation to ten months.

2) A brother-in-law of the above patient, a physician with a severe endogenous depression following a second coronary occlusion, was so impressed by his relative's response that he voluntarily came for help. While he was quite pessimistic, he stated, "I have to see for myself what this new drug is all about." His response, while not as dramatic, was satisfactory and improvement was maintained on follow-up evaluation. At one time his blood pressure dropped from 170/110 to 88/60 without apparent aggravation of the coronary disease.

3) A severely depressed 54 year old male, two weeks post-cholecystectomy, was brought to my office. He had lost approximately 30 pounds. Due to his operation electrotherapy appeared contraindicated. Fifty mgms marsilid three times daily was prescribed and after one week he began to be more at ease and slept better. Urinary retention due to prostatic hypertrophy developed during the fourth post-operative week. Urological consultation suggested immediate operative intervention. He was continued on marsilid, and following the suprapubic prostatectomy he made a complete remission from his depression.

4) This patient exhibited the most dramatic response to marsilid in my experience. He weighed 180 pounds and was four feet 8 inches tall. His blood pressure ranged between 240/120 to 260/140. He had been under the care of a cardiologist because of two severe coronary occlusions. To relieve precordial distress he frequently resorted to nitroglycerin. The cardiologist considered electroshock treatment contraindicated. I carried him in supportive psychotherapy with occasional intravenous sodium amytal for 9 months. By reason of repeated suicide threats I suggested hospitalization but he was adamant against such care. I saw no alternative but to try marsilid. Within ten days the depression was reversed and he was able to take a trip to a convention on the west coast. He has gradually reduced his marsilid to 10 mgms once daily. His blood pressure while on larger doses of marsilid dropped to 160/90. His cardiologist was amazed at the change in his hypertension, particularly since he had been on vasodepressive drugs for an extended period.

I might add that my electroshock case load has decreased considerably since using this drug. However, a word of further caution is in order. In one severely depressed patient electroshock treatment would have been indicated were it not for an extremely high diastolic pressure. I decided to temporize by using marsilid, since she refused hospitalization. Two days after her first visit she committed suicide with carbon monoxide. As with all new drugs, caution is necessary in its more expanded use.

East Orange, N. J.

Use of Iproniazid (Marsilid)

ALFRED GALLINEK, M.D.

I have used iproniazid extensively for over five months and I have reached the conclusion that it is an extremely potent and useful drug. Like ECT and other drugs used in psychiatry its applicability cuts across our diagnostic categories. It appears to be indicated wherever there is a state of severe inhibition, withdrawal and depression. I was most impressed by its effect in a complex schizophrenic syndrome of more than five years' duration. This patient had been under my uninterrupted observation for more than four years. He had had intensive psychotherapy with limited success. Several courses of extensive ECT ameliorated catatonic episodes for a short time. The patient

always had remained completely withdrawn, autistic with rigid affect, with occasional impulsive actions and severe disturbance of his thinking mechanism. After four weeks of iproniazid he became mildly euphoric and exceedingly active in an orderly fashion. He has resumed contacts with his family and friends and is working successfully.

However, as soon as the daily dosage of 150 mg is lowered his symptoms reappear. When functioning well he has a feeling that his disease is still present but somehow is in the background. He still can at will bring on his old symptomatology.

In this patient as well as in successfully treated depressive patients it is not entirely correct to speak of attainment of a normal affective level. The patients appear to be euphoric (hyperthymic).

An interesting question is whether ECT could be safely administered in conjunction with or immediately after iproniazid. In some patients iproniazid does not seem to show any marked effect before at least three weeks. In all acute and serious psychotic depressions, particularly those with a suicide risk, it, therefore, cannot substitute for ECT. The fact that the above mentioned schizophrenic patient retains his symptoms "in the background" while feeling and functioning well, and that the full-fledged syndrome reappears with lowering of the dosage appears to indicate that iproniazid does not affect the basic pathologic mechanisms.

New York, N. Y.

Iproniazid in Psychiatric Treatment

CARL BREITNER, M.D.

Since iproniazid is described as a psychic energizer and a stimulant to the appetite, we have attempted lately to use it in the treatment of mute catatonic schizophrenics. The results have been encouraging, particularly in those cases that had responded to ECT, but would relapse when ECT was discontinued.

We have a number of patients who were hospitalized for a long time, who, with the use of Marsilid, have left the hospital apparently well.

It is also considered significant that since we have been using this drug not a single case required tube feeding. Unfavorable side-effects have been minor, but one patient developed a seizure and the drug was discontinued. When started again on a lower dosage, she again had a seizure.

The preferred dosage of iproniazid is 50 mg. t.i.d. to start with. When the patient improves or hyper-reflexia develops we reduce the dosage.

Phoenix, Ariz.

An Effective Oral Chemotherapy for Melancholia—Iproniazid

THEODORE R. ROBIE, M.D.

For nearly 20 years the most effective treatment for severe depressions has been electroshock therapy (EST). While it is recognized that this therapy involves certain skeletal hazards, nevertheless, the relative infrequency of fracture induced many psychiatrists to administer this therapy, and thus many thousands of persons are alive today, who might have taken their own lives. In the last few years muscle relaxants have practically eliminated the fracture hazard and more recently additional safeguards have been added which reduce immeasurably the degree of hazard involved in EST.

It now appears that iproniazid alleviates melancholia in a good many depressed patients, thus avoiding the use of electroconvulsive treatment. Although Kline and his co-workers in 1957 first described the improvement induced in depressed patients by this compound, other physicians had previously described euphoric effects induced in tuberculous patients. I became aware of the beneficial effects of iproniazid shortly before Dr. Kline's paper was presented in Syracuse. I first used it on depressed patients, particularly those who were malnourished or who had physical handicaps that made electroshock therapy hazardous. Depressed patients with suicidal drives were immediately given EST, since there is a latency period of two to four weeks in many cases, before the definite euphoriant effects of iproniazid become manifest.

In some cases iproniazid has been administered simultaneously while the EST course

was in progress. In one such case we observed a much quicker recovery than in several previous depressions.

So far over 65 patients have been treated with iproniazid and from this experience it can be said that improvement has been observed in some cases previously resistant to other methods of treatment.

I can best illustrate the encouraging results by describing some of the cases.

Case 1. One of the most satisfying results is that of a 38 year old woman who had been depressed for 6 months. She had been unsuccessfully treated for malnutrition for several years. She was brought to a good remission by a full course of EST just before iproniazid came to my attention. However, malnutrition persisted and since she was 28 lbs. underweight the probability of recurrent melancholia was anticipated and she was started on this drug after her EST course. It has been a most satisfying clinical experience to watch this patient slowly regain 23 lbs. Five months after iproniazid was started, she has recovered her normal weight level and she enjoys a normal state of well-being.

Case 2. This patient showed a rapid and striking improvement on iproniazid. This 57 year old woman had suffered an attack of severe melancholia seven years previously, which required a course of EST. She came to me demanding that she be given EST immediately. In her words, "I seem to have lost my faith in everybody. I keep thinking of all the things I have done wrong in my life and right now I don't even want to live. I think my husband would be much better off without me." EST could not be administered because of a serious cardiac complication which had developed since the original course of shock treatments. She had come through that first course of EST without difficulty. Two other psychiatrists had seen her during the present depression. Each of them had given her one EST during each of which she nearly died. There had been a six months interval between these two treatments. I placed her on iproniazid therapy. Unfortunately she soon developed a considerable degree of edema of both feet. This necessitated halting the iproniazid causing regression to a more severe depressed state. However, on adequate cardiac and diuretic therapy, the edema cleared and she was again started on iproniazid with smaller dosage. This time with the diuretic medication continued she did not show any edema. In less than four weeks the depression remitted. Improvement has continued without interruption for six months and this patient has remained well on a minimal dosage of iproniazid.

Case 3. The most interesting case so far encountered was a recurrence of extreme melancholia with seclusive and paranoid elements in a 62 year old patient. This woman, who has lived alone since her husband's death five years before, would frequently arouse the neighborhood by agonizing screams during the night. These she insisted were caused by her uncontrollable loneliness. She had been sent to a psychiatric hospital before I saw her, but on returning home her nocturnal screaming episodes recurred. She was brought to me two years ago by a nurse and ultimately consented to ambulatory EST. This induced an apparent remission within a month but a few months later she partially relapsed.

After causing innumerable squabbles in her neighborhood, she finally returned to me but refused to take EST. I tried various tranquilizers for three months but had no success in stopping the commotion she caused. Then I decided there was nothing to lose by trying iproniazid even though agitated patients supposedly are worsened by the drug. After four weeks she admitted she felt fine and the agonizing nocturnal outcries ceased as did her neighbor's complaints about her. With recovery came the accompanying refusal to visit me further because she was "all well now."

Case 4. Three years ago I was called to a hospital in a nearby city to see a 59 year old man who had attempted suicide by swallowing a large number of barbiturate pills. He had been in coma for 40 hours. Continuous cerebral electrostimulation for the next 40 hours brought him back to consciousness and then a course of electroconvulsive treatment over the next four weeks relieved him of his severe depressive psychosis. But in a few weeks the depression returned and another suicidal attempt was feared. At this point the patient agreed reluctantly to the resumption of electroconvulsive treatment at regular intervals and it was possible to maintain him at near normal for the next two years. I was anxious to start him on iproniazid but hesitated because of his severe hypertension ranging from 220/118 to 272/128. However, on hearing that in a few other patients this drug had reduced high blood pressure, I placed him on iproniazid with the hope of eliminating the necessity of maintenance EST every third week. This drug not only improved his depression and made possible the elimination of electroshock for the past six months but at the same time reduced the elevated blood pressure. Each month that passes with no need for EST, strengthens the view that a permanent recovery has been induced.

Case 5. A depressed female in her early forties had received two courses of EST in a mental hospital. When I saw her in June 1956 she was severely depressed and in need of EST. She was given a course of 13 treatments and although she improved, the degree of remission was only fair. In February 1957 her depression had recurred and another course of EST had to be instituted. Her melancholia was so severe she had to be given double treatments for the first three days of the second course of 12 treatments. She was carried then on maintenance therapy for some time. Later, she was started on iproniazid in the hope that the maintenance EST could be discontinued. She had

been receiving treatments every two weeks and by the time the next EST should have been given she was sufficintly improved to make it possible to postpone electric treatment. She was continued on the drug and has maintained adequate improvement to this date so that she has had no EST whatever since April 6, 1957 (a period of nine months).

There have been certain trying complications in this case: During the second month she developed a rapid increase in blood pressure to the degree of hypertension with severe headaches accompanied by marked constipation. Accordingly she had to be taken off the drug until the constipation cleared up. After that it was possible to resume with smaller dosage. At another occasion she developed some ankle edema and again her iproniazid dosage had to be stopped, but this cleared up relatively quickly on Diamox therapy and the iproniazid was again resumed.

Discussion and Complications

The ingestion of iproniazid does not preclude psychotherapy or make it in any way unnecessary. It is very important to realize that this medication, with the improved sense of well-being which it assures, increases in a large degree the rapport with the psychiatrist and makes it much easier for the patient to initiate the spontaneous discussions which are so helpful in psychotherapy.

Iproniazid protects serotonin from monoamine oxidase, i.e., it is an amine oxidase inhibitor. Only recently has it been recognized that serotonin is probably an energetic psychic stimulant. The simultaneous release of nor-epinephrine by adequate amounts of pyridoxine further potentiates and accentuates the energizing effect.

Ankle edema is a fairly frequent occurrence following iproniazid therapy. However, it usually recedes in a few days by discontinuing the drug and administering Diamox for seven to ten days. Then iproniazid can be safely resumed in smaller dosage and edema usually does not recur.

Too rapid gain in weight may result in distortion of the patient's appearance. One very slight woman gained 13 lbs. so rapidly that she appeared pregnant due to the apparent liver enlargement. A lower dose of iproniazid corrected the gain in weight. A rare complication which I have not encountered but which has been reported is a agranulocytosis. Therefore, a complete blood count should be done at the start of treatment for comparison with later blood findings.

Rarely tingling or hypesthesia in the extremities may be reported. As a rule pyridoxine, 2.5 mg. t.i.d. will obviate this complaint. Also, pyridoxine orally or intravenously will overcome nausea that may develop when iproniazid has been ingested over a considerable period.

Also rare is an increase in blood pressure level to a point where hypertensive headache may be experienced. Should this occur medication should be stopped for two or three days and then resumed on half former dosage. This usually clears up the headache. The blood pressure should be recorded regularly in any patient taking iproniazid.

The complication met with most frequently is impotence in males and frigidity in females. This may be reported relatively soon after starting the drug. This is a serious drawback and may cause the patient's refusal to continue the drug despite realization that the depression may recur. In such instances resort to electroconvulsive therapy may become imperative since it is well known that EST often brings a return of potency in depressed patients. While impotence is not usually a welcome complication, in one case it proved a blessing in disguise. A woman whose depression had been aggravated by the lack of sexual outlet because of the husband's impotence had become quite passive and non-complaining about this void in her life and it has undoubtedly played some part in sustaining her remission. In direct contrast, there are rare instances of hyper-erotic activity that have been reported by others, and I have encountered one striking case in my series of less than 100 cases. In a schizo-thymic male, extraordinary capacity for prolonged coitus developed along with marked increase in frequency.

Since patients may be led to think of iproniazid as a sedative or tranquilizer or an energizer or euphoriant, it is important to instruct patients to consider iproniazid as a deficiency supplement.

Conclusions

1. Iproniazid will not eliminate the need for EST, but it will reduce the number of patients receiving electroconvulsive treatment.

2. Unless the melancholy person is aggressively suicidal, a four weeks' trial should be given on iproniazid before EST is initiated.

3. If suicide is imminent, modified EST must be the treatment of choice unless there are extreme physical contraindications.

4. The patient must be seen frequently at the beginning of treatment to determine whether depression is receding. Constant supervision by the family or a nurse is indispensable or there will be an increase in suicides.

5. In many patients the full effects of iproniazid will not become manifest until three or four weeks. This must be kept in mind.

6. One of the best uses of iproniazid will be to prevent future depressions; by starting it immediately following any course of EST it is believed future need for EST might be obviated.

7. The major advantage of this drug to psychiatry will come from the enhancement of psychotherapy, while at the same time counteracting melancholia.

ADDENDA

In the six months' interval since this paper was completed the number receiving this therapy has doubled and further observations should be noted. These are of significance since others have reported hepatitis as a complication of Marsilid therapy (I have seen none) and it is alleged that some deaths have been caused thereby. However, the pathologists who have studied the necropsied livers insist that hepatitis is indistinguishable from that found in virus hepatitis.

In my experience, hypotensive effect is almost universal when this chemical is given. This can be an advantage, but the degree can be controlled by adjusting the dosage downwards as the patient improves during the three to four weeks necessary to induce a remission. This may prevent hepatitis if it is caused by hypoxia arising from the hypotension, allowed to reach an extreme degree by excess Marsilid dosage. It should be emphasized that frequent blood pressure recordings are just as essential when a patient is taking Marsilid as it is when the patient is under treatment for hypertension! (See Proceedings: Society of Biological Psychiatry May 1958.)

East Orange, N. J.

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Chemotherapy of Depression

MEPROBAMATE COMBINED WITH 2-DIETHYLAMINOETHYL BENZILATE HYDROCHLORIDE (BENACTYZINE) *

LEO ALEXANDER, M.D.

Remarks

This study has been carried out in 35 consecutive patients presenting symptoms of depression sufficiently severe to warrant the consideration of physical treatment methods. The tablets used contained either 200 mg of meprobamate and ½ mg. of benactyzine, or 400 mg. of meprobamate and 1 mg. of benactyzine. The initial dose was usually 400 mg. of meprobamate and 1 mg. of benactyzine four times daily, the smaller single dose having been found ineffective as an initial dose. If then necessary, the dosage was gradually increased up to 1200 mg. of meprobamate and 3 mg. of benactyzine, four times daily. As improvement supervened, the dosage was gradually reduced to below the minimum initial dosage and this then gradually tapered off by reducing the number of daily doses. The usual supportive psychotherapy, including clarification of traumatic issues, was administered concurrently.

Of the 35 depressed patients treated 20 achieved a state of complete or social recovery within one to 25 weeks, the average being eight weeks. There were 26 psychotic depressions of the manic-depressive or involutional type while nine were neurotic depres-

sions. The duration of the psychotic depressions varied from two weeks to two years, the average being 13 months; that of the neurotic depressions varied from one month to two years, the average being nine months. It is of interest to find that the recovery rate for these two groups is identical. Of the psychotics 15 recovered, making a recovery rate of 58%; while five of the neurotics recovered, making a recovery rate of 55%. The recovery rate for the total group was 57%. The duration of treatment until recovery supervened was almost identical. It varied from one to 25 weeks for psychotic depression and from two to 23 weeks for neurotic depression, the average being eight weeks for both groups.

*Supplied in the form of "Deprol®" by Wallace Laboratories, New Brunswick, New Jersey.

Boston, Mass.

Summary of Round-Table Discussion of Newer Psychiatric Drugs

Moderator: WILLIAM L. HOLT, JR., M.D.
Albany, N. Y.

In contrast to most recent clinical research reports on the tranquilizing effects of newer psychiatric drugs, this Round-Table Discussion emphasized the greater effectiveness of euphoriant psychic energizers in relief of severe depression and anergic withdrawal states. The report by Theodore R. Robie, M.D., on iproniazid, asserted electro-shock should be reserved for the actively suicidal patient only and no longer had a place for maintenance of recovery from depression. His report paid attention to the occurrence of psychosexual changes, impotence and frigidity being noted. The moderator's clinical experience included a case of virtual satyrism related to the use of iproniazid. Other complications have included blood-pressure changes (usually falling), ankle edema, rash, convulsions, dysuria, jaundice, neuropathy (including scotoma from optic neuritis) and dependency on the drug. Robie cited agranulocytosis from the literature of its use in tuberculosis therapy but no instances were reported by those discussants present with a combined total of several hundred psychiatric cases. Agreement as to the high order of effectiveness characterized the reports of Theodore Robie, M.D., William Furst, M.D., Carl Breitner, M.D., Alfred Gallinek, M.D., and this moderator. That therapeutic effect may be delayed three to four weeks when 150 mgm a day are given was generally agreed, yet other patients respond in a shorter time.

The value of combining energizers with tranquilizers received comment. Dr. Santino Lando reported on the value of dexedrine, combined with chlorpromazine, in patients with little or no anxiety. Dr. Leo Alexander reported on combining meprobamate with benactyzine in treatment of depression. General agreement was expressed as to energizers being contraindicated when anxiety was prominent. Simultaneous use of ritalin or dexedrine with iproniazid was described by Dr. Furst. He, as well as your moderator, noted that electroshock therapy for the more severe depressions could be combined with iproniazid therapy with a lesser amount of electroshock than would ordinarily have been required. The most controversy centered about the duration of use where depression was treated with energizing drugs alone, as relapse was common if the drug was stopped before the depressive state might be expected to have gone into remission spontaneously. The answer to this thorny question must await the accumulation of cases with longer periods of follow-up. Only one worker, Lothar Kalinowsky, M.D., had failed to note a decrease in indications for electro-convulsive therapy.

3. Experimental Investigations

Effect of Current Intensity on Cardiovascular Response to Transcranial Stimulation

CHARLES H. ELLIS, PH.D., and
KENNETH I. COLVILLE, PH.D.

The rise in arterial pressure produced by electroconvulsive therapy has been studied by several investigators with a variety of experimental approaches (Silfverskiöld and Amark, 1943; Brown *et al.*, 1953; Holmberg *et al.*, 1954). The pressor effect is usually ascribed to a generalized involvement of the sympathetic nervous system. Weil-Malherbe (1995) showed that the amount of epinephrine and norepinephrine in the plasma is increased following ECT. The magnitude of the hypertension induced in dogs by transcranial stimulation is diminished by adrenalectomy and is abolished by spinal section above the level of sympathetic outflow (Colville *et al.*, 1958).

The parasympathetic nervous system is also activated by ECT, resulting in an initial bradycardia and transient hypotension. Clinical employment of atropine to prevent the intense bradycardia caused by ECT was first advocated by Bellet, Kershbaum and Furst (1941), and it is now commonly used to prevent increased parasympathetic activity in ECT (Bankhead, Torrens and Harris, 1950; Richardson *et al.*, 1957). In animals both bradycardia and hypotension are abolished by vagotomy (Ivy and Barry, 1932; Frostig *et al.*, 1944; Brown *et al.*, 1952).

Both sympathetic and parasympathetic nervous systems are stimulated by currents of the intensity commonly used in clinical ECT. The cardiovascular response is complex, and the problem of demonstrating the various component mechanisms within this generalized pattern is quite provocative.

In view of the probable supramaximal character of the stimulus in ECT, it is conceivable that by using stimulating currents of lower intensities a certain amount of separation of the various elements of the total autonomic response to transcranial stimulation might be achieved.

From the Wellcome Research Laboratories, Tuckahoe, N. Y.

Methods and Results

Dogs have been used throughout the present investigation. The animals were anesthetized with pentobarbital sodium (Nembutal®), 30 mg./kg. intraperitoneally. A tracheal cannula was routinely inserted to permit speedy application of positive pressure artificial respiration whenever spontaneous ventilation became impaired. Systemic arterial pressure was recorded from a cannulated carotid artery, using a Statham P-23AA transducer and Sanborn Poly-Viso direct writing recorder. Succinylcholine chloride (Anectine®) was routinely used to avoid complicating factors related to contractions of skeletal muscles. The succinylcholine dosage was 300 mcg./kg.

Electrodes of 2 inch diameter were placed over the temporal areas of the dog's head and fastened in position with gauze bandage. An electrode jelly was used to assure electrical contact. The usual DC resistance between the electrodes was about 10,000 ohms.*

Because of the close relationship between the present investigation and clinical ECT, a standard Medcraft ECT Unit was used to provide the stimulating currents. This instrument is not equipped with a means for controlling current intensity other than a stepwise regulation of the sinusoidal AC voltage applied to the electrodes. Its range is from 70 to 170 volts. In order to study the effects of submaximal currents it was necessary, therefore, to provide for actual measurement of the current during its flow. This was accomplished by inserting an AC milliammeter of appropriate sensitivity in series with one of the electrodes. Currents from 10 mA to 1150 mA were obtained by reducing the voltage at its source (the stim-

*Although the DC resistance measured about 10,000 ohms, the "functional" resistance calculated from the measured current and measured voltage was variable, falling rapidly from about 2,000 ohms at 10 mA to about 200 ohms at 100 mA with only minor changes from that level as higher currents were used.

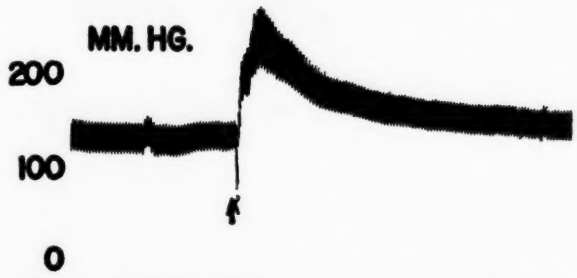

Fig. 1. Arterial pressure response to supramaximal transcranial stimulation. At arrow a current of 900 mA was applied for 1 sec. Time = min.

ulator) or by inserting resistance in series with the animal.

Hemodynamic Investigations: Study of the hemodynamic effects of currents from a minimum of 350 mA to at least 1150 mA showed a qualitatively characteristic pattern. As can be seen from Fig. 1, a current of 900 mA, for example, caused first an immediate precipitous fall in arterial pressure which was quickly followed by a marked hypertension persisting for several minutes. Colville *et al.* (1958), confirmed that the initial fall is of parasympathetic origin since it is abolished by vagotomy, atropine, or by other agents which block parasympathetic activity.

Experiments with smaller current intensities disclosed several other patterns of response. Stimulation with currents below 17 mA caused no changes in arterial pressure. As current intensities were increased above this level several discrete patterns of response were encountered. The first pattern to emerge was a slow depressor response (Fig. 2A) unlike the transient and precipitous fall observed with markedly higher currents. It sometimes reached a magnitude of 50 mm. Hg. and lasted 20 to 30 seconds. This pattern occurred with currents above 17 mA and was the sole response in the range from 17 mA to a poorly defined upper limit ranging from 90 to 170 mA. The amplitude

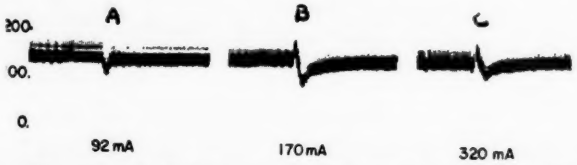

Fig. 2. Arterial pressure responses to transcranial stimulation with currents of graded intensities. A = 92 mA, B = 170 mA, C = 320 mA. Time = min. Pressure = mm. Hg.

of this hypotensive response was somewhat variable from animal to animal and appeared to reach a maximum in any animal in the range from 30 to 60 mA. The response gradually diminished as currents were increased above these levels.

When currents of 50 mA (falling in the range of this unmixed depressor response) were applied to animals in which one hind limb was being perfused artificially, the fall in arterial pressure was accompanied by a corresponding fall in perfusion pressure (Fig. 3). The perfusion experiments have been described in detail by Colville *et al.* (1958), and consisted essentially of cannulation of one femoral artery with two polyethylene catheters, one directed toward the heart, the other, peripherally. A Sigmamotor perfusion pump drew blood from the cardiad catheter and delivered the blood peripherally at a constant rate of flow. Since the propulsion of blood was controlled by the pump, it was independent of changes in either activity of the heart or of changes in systemic blood pressure. Changes in perfusion pressure, therefore, would reflect changes in the resistance of the vascular bed; reduction of pressure would indicate peripheral vasodilatation, elevation of pressure, peripheral vasoconstriction.

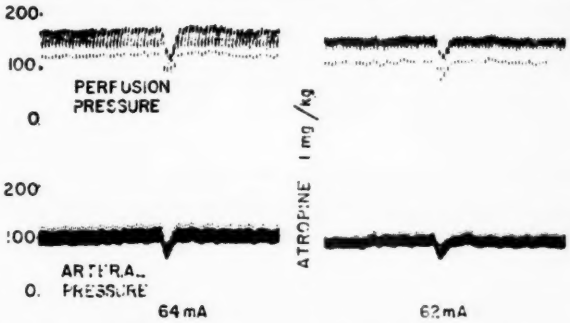

Fig. 3. Effect of atropine on responses of arterial pressure and hind limb perfusion pressure to minimal intensity transcranial stimulation. Time = min. Pressure = mm. Hg.

The slow fall in arterial pressure coincided chronologically with a dilatation of the vessels of the leg as indicated by the simultaneous fall in both perfusion and arterial pressures. Neither the slow hypotension nor the perfusion pressure response was modified by atropine (See Fig. 3), but both were abolished by tetraethylammonium chloride.

Somewhere between 90 mA and 170 mA a second and more complex type of response pattern was elicited (Fig. 2B). This response was diphasic and was characterized by an increase in arterial pressure (without any initial fall) followed by a short period of hypotension. The ampiltude of the pressor portion of the response was small at near-threshold currents, but became more pronounced when higher currents were used. The duration and magnitude of the secondary fall in arterial pressure was of about the same order as that which was produced by low current stimulation. As with the lower currents, the depressor response was not blocked by atropinization. Moreover, limb perfusion experiments showed that peripheral dilatation was present during the depression in arterial pressure.

Two experiments have shown marked increase in pulse pressure during this diphasic response. For instance, when a current of 156 mA was used (Fig. 4), a marked increase in systolic pressure was seen, although a simultaneous fall in diastolic pressure was present.

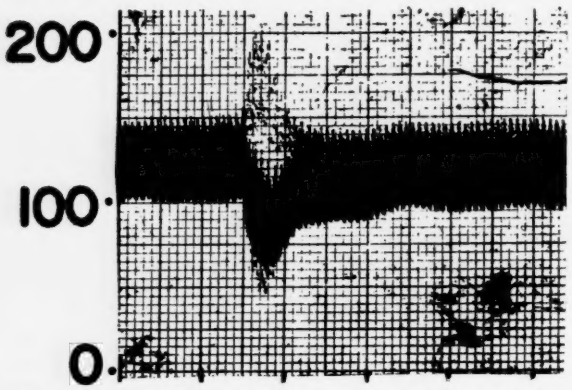

Fig. 4. Simultaneous increase in systolic and decrease in diastolic arterial pressures induced by transcranial stimulation of 156 mA intensity. Time = min. Pressure = mm. Hg.

When currents of 200 mA or above were administered, a third type of response resulted in which the diphasic response was preceded by a transient precipitous depressor effect. This fall in arterial pressure was abolished by atropine or vagotomy. In the experiment shown in Fig. 2C it can be seen that the response to 320 mA was essentially similar to that induced by a current of 170 mA (Fig. 2B) except for the presence of the initial hypotension.

Above 350 mA the pattern changed only by the disappearance of the secondary depressor phase and an intensification of the pressor response. With these higher currents limb perfusion pressures were increased, but only after a delay of about 30 seconds.

Discussion

From the above experiments it appears that several discrete hemodynamic factors are contributing to the cardiovascular response to transcranial stimulation. By studying the effects of currents of graded intensity it has been possible to separate the total response into some of its elements.

The slow hypotensive response to low current intensities is the most sensitive mechanism, inasmuch as it alone was present when currents below 90-170 mA were applied. This response has been shown to involve dilatation of the vessels in the perfused hind limb, and, although experiments have not included other vascular beds, it would seem unlikely that dilatation would be limited to just the one bed studied. Since any mediator substance would have been delayed in its arrival in the perfused limb by passage through the pump and tubing, the immediate onset of the fall in perfusion pressure would suggest a direct nerve-induced vasodilatation.

Since the depressor response is blocked by the ganglionic blocking drug, tetraethylammonium chloride, it would appear to be of autonomic origin; this fact, plus the fact that atropine fails to block the response, points to a sympathetic rather than a parasympathetic mechanism. The existence of sympathetic vasodilator nerves has been well established since such fibers were first postulated by Dale to explain the reversal of the epinephrine response.*

Stimulating currents of slightly higher intensity exhibited a second stimulus-response threshold which consisted of a diphasic change in arterial pressure (Fig. 2B). The rise in pressure could be accounted for either by a selective vasoconstriction in some vascular bed other than that of the hind limb, or by direct increases in heart force. The

*For a more detailed discussion of the control of vasomotor responses by the central nervous system, reference to the recent monograph by Lindgren is suggested (Acta Physiologica Scandinavica, 1955, Sup. 121).

perfusion experiments indicated that in the hind limb peripheral vasodilatation was present with currents as high as 320 mA. Since this one vascular bed so consistently showed vasodilatation, it would be surprising to find vessels in other areas so markedly constricted as would be necessary to account for the pressor response.

As this well defined rise in systolic pressure occurred in several experiments at precisely the same time as a fall in diastolic pressure, the increase in systolic pressure is probably due to a direct positive inotropic action on the heart. The fall in diastolic pressure, which would be influenced only by changes in peripheral vasomotor tone, is indicative that peripheral dilatation is still taking place. Such positive inotropism could result from either stimulation of the augmenter nerves to the heart (Rohse *et al.*, 1957; Cotten, 1953; Randall and Rohse, 1956; and Anzola and Rushmer, 1956), or from the direct inotropic action of released epinephrine or both.

The fact that the depressor response to low currents becomes gradually less marked as the pressor thresold is neared suggests a transitional cancellation phenomenon in which the pressor and depressor responses are being added algebraically. This could offer in part an explanation for the less well defined threshold current level for the pressor response in Fig. 2B.

A third stimulus-response pattern is characterized by vagal stimulation. It is quite well defined, and varies little from animal to animal. This threshold for activation of the vagus centers is about 200 mA. Currents above this level cause a brief but profound bradycardia which results in the transient initial hypotension seen in Fig. 1. Unless atropine has been administered or the vagus nerves have been sectioned, this hypotension is characteristic of all responses from currents above the 200 mA threshold.

With currents above 350 mA the response is further characterized by a disappearance of the secondary hypotensive phase (Fig. 1), probably because of mobilization of vasoconstrictor mechanisms, either directly nerve-induced or humoral. When these higher currents are used for stimulation a rise in perfusion pressure in the hind limb indicates that the vasodilatation of the peripheral vascular bed was replaced by vasoconstriction. The fact that this increase in perfusion pressure was delayed suggests that humoral vasoconstriction was involved. This would be expected in the light of investigations such as those of Weil-Malherbe (1955) showing a marked increase in circulating epinephrine and norepinephrine after ECT, or of Colville *et al.* (1958) showing that the response is reduced by adrenalectomy and abolished by cord transection just below the point of separation of the vagus and sympathetic trunk.

Summary

Using low and intermediate current intensities for stimulation it has been possible to demonstrate more or less selective activation of one or another of the autonomic mechanisms whereby changes in arterial blood pressure can be induced by transcranial stimulation. With higher currents the problems of identification of discrete elements in the mechanisms becomes increasingly difficult, until, with maximal currents, about all that can be said is that a generalized autonomic discharge involving both sympathetic and parasympathetic systems occurs.

The discrete thresholds for eliciting some of the elements of this generalized autonomic discharge have been shown to result in first, a nerve-induced peripheral vasodilatation resulting in a fall in arterial pressure. At slightly higher current intensities an increase in inotropic heart action results in the addition of a pressor response of cardiac origin. At still higher currents bradycardia of vagal origin introduces an initial transient hypotension, and with maximal current intensities vasoconstrictor mechanisms are activated which predominate over the vasodilator responses peripherally. This vasoconstriction reinforces the positive inotropic response to cause a marked hypertension.

Authors' Note: The technical assistance of John C. Schroder, B.S., in this study is gratefully acknowledged.

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COMMENTS ON THE PAPER BY DR. ELLIS AND DR. COLVILLE

EDWIN J. DE BEER, PH.D.

The interesting data presented by Dr. Ellis and Dr. Colville indicated that the pattern of the cardiovascular response may vary with the intensity of the electrical, transcranial stimulus. At least three factors affecting the circulation were identified as contributing to the complex blood pressure patterns. At low current levels, for example, the principal effect seemed to be a dilation of the peripheral blood vessels with a resultant fall in blood pressure. When the stimulus intensity was increased, the vagus also participated. At the higher current levels a third circulatory effect involving the secretion of epinephrine could be detected. One wonders if, by proper design of the stimulus with regard to such additional factors as wave-form, pattern, duration, etc., relatively specific responses might not be isolated. If this proved to be the case, it would seem likely that new, additional information could be obtained in pharmacological and clinical research.

The analysis of the cardiovascular effects of transcranial stimulation into component factors leads to the hope that additional remedies can be found which would control side effects. As the situation now exists, succinylcholine will prevent dangerous convulsive contractions of skeletal muscle. Atropine reduces excessive salivation and ameliorates vagus effects. The work presented here this morning reveals that we are still faced with an acute hypertension of considerable magnitude. It seems quite reasonable to expect that a short-acting powerful drug may be found which will control the sympathetic discharge and thus offer protection against the sudden, sharp increase in blood pressure.

Carbon Dioxide in the Treatment of Post Concussion Syndromes

MICHAEL M. GILBERT, M.D., PH.D.

The post concussion syndrome presents a perplexing problem for several reasons. Firstly, quite often the diagnosis is difficult inasmuch as most of the findings are purely

subjective. There are occasional objective signs such as an abnormal electroencephalogram, disturbed vestibular function, increased spinal fluid protein, the Muck Adrenalin-Sondenversuch Test,[3] and psychological tests.[8] However, these objective signs appear infrequently and a diagnosis is more often made without the tests and even in the absence of these findings. Generally, it is made on the findings of a combination of these symptoms following a disturbance in consciousness from a head injury: headache, irritability, emotional instability, dizziness including vertigo or giddiness, blurring of vision, depression, fatigue with asthenia, occasional tinnitus, recent memory impairment, poor tolerance to alcohol, lack of ability to concentrate over prolonged periods, and loss of libido.

Secondly patients with post concussion syndromes are usually involved in claims and litigation. As a consequence of the economic factors of the case, its is all too frequently assumed that all patients are motivated by financial gain, and are either assuming or exaggerating symptoms.

Finally treatment is often unsuccessful, in most cases requiring a prolonged course of three to 36 months. The usual sedatives and analgesics are prescribed without any considerable help. Prostigmine[10] has been used with varying success, but this therapy has not been of consistent value. There is no specific treatment.

A treatment method described in this paper has shown considerable promise and is based on the following rationale:

Courville in his treatise "Commotio Cerebri"[3] has shown that there are definite histologic changes occurring with the post concussion syndrome. These changes consist mostly of chromatolysis with progressive dissolution of the tigroid granules in the nerve cells of the cerebral cortex. There is also neurofibrillar degeneration and nuclear alterations affecting the chromatin material. In addition to these cellular changes, Courville describes multiple focal lesions characterized by areas of cell loss, either in the cerebral cortex or nuclear masses of the brain stem, which appear to be the result of anoxia, incidental ischemia due to vasospasm, or a prolonged drop in blood pressure due to primary shock of concussion or subsequent traumatic shock. In addition to these direct cellular and structural alterations, Courville describes a third change incidental to edema of the brain. This is manifested histologically by acute swelling of the oligodendrolglia and increased vacuolization of the choroidal and ependymal epithelium as a consequence of the cerebral edema. It also is evident that there is a decided disturbance of the vasomotor regulatory mechanism as reflected by the symptoms of postural syncope and vertigo. It follows then, that the post concussion syndrome is due to an organic lesion rather than a functional disorder.

In consideration of the above neuropathological changes it occurred to the author that carbon dioxide inhalations may be of value.

Carbon dioxide therapy was introduced by Meduna in 1948 for the treatment of neuroses.[11] Meduna based his rationale primarily on Lorente de No's work[7] on the isolated nerve. Lorente de No showed that carbon dioxide, in significant concentration, raised the threshold of stimulation, increased the membrane potential, increased the ability of the nerve to conduct trains of impulses, and delayed appearance of fatigue in the stimulated nerve. De No also demonstrated that the effect of the CO_2 on the membrane potential is proportionate to the logarithm of its concentration. Dusser de Barenne, McCulloch and Nimms[4] found that the low pH of the cortex caused by CO_2 was associated with low electrical activity and a decreased excitability of the cortex. Meduna extended this to include the Eccles-Brooks hypothesis[2] wherein the increase in membrane potential lowers the excitation of the Golgi cells and so converts many excitors into inhibitors thus augmenting inhibition.

Other research has shown additional effects of CO_2 on nerve tissue. It is known from the work of McLennan and Elliot[9] that carbon dioxide destroys acetylcholine by lowering the pH in the brain. Moreover, Bain and Klein's[1] work indicates that the concentration of brain lactate and pyruvate bears an inverse relation to the levels of carbon dioxide, hydrogen and oxygen, in the cere-

bral blood. They felt that the "resulting increase in blood flow and oxygen tension (brought about by the 30% CO_2 and 70% O_2 mixture) enabled the brain to more clearly balance energy demands with oxidative processes and as a consequence less lactate was formed and high energy phosphate reservoirs were not depleted."

In addition to the effect of carbon dioxide on nerve tissue per se, its effect on cerebral blood flow has been clearly demonstrated. The works of Kety and Schmidt[5] and Scheinberg[12] have demonstrated that carbon dioxide is the most potent cerebral vasodilator there is, and that concentrations of carbon dioxide above 10% produce profound increases in total cerebral blood flow. Hence, CO_2 produces a double-barreled effect wherein the high CO_2 tension effect on the cells is potentiated by an increased blood flow with increase in available oxygen as well as whatever beneficial effects which may result from increased cerebral circulation. As a consequence, the chronic vasospasm described by Courville could well be ameliorated. Consideration also should be given to the fact that arterial O_2 tension is increased by the treatment and this may be of therapeutic significance.[11]

In consideration of the above-mentioned effects of administration of carbon dioxide-oxygen inhalations, it was felt that this treatment method would provide a multi-edged weapon in the correction of the underlying cellular and vaso-motor changes in the post concussion syndrome.

Procedure

Carbon dioxide and oxygen in separate tanks is supplied and mixed through a Y tube so that the concentration of each gas can be modified. The patient, after preliminary instruction as to what he would expect to feel, is started on 100% oxygen for a few breaths until he adjusts to the mask and inhalation. Then about 5% CO_2 is added to the mixture to permit the patient to adjust to the odor of the gas. After a few whiffs, the CO_2 concentration is increased gradually until there is a 50% O_2 and a 50% CO_2 mixture given at about 8-10 liters per minute from each tank. This results in a profound hyperpnea and within ten to twenty inhalations the patient usually lapses into coma. This is the end point of the treatment. The mask is removed and the patient allowed to recover spontaneously. Treatments are given three times weekly. It is to be noted that this treatment method differs from Meduna[11] and LaVerne[6] in that the former uses a 30-70% mixture and the latter a rapid coma technique using 100% CO_2 in one or two inhalations. It is felt that the method described in this paper results in less anxiety in the patient since unconsciousness is reached rapidly and permits continuation of the treatment. This is an important consideration as many patients, if not properly handled, will discontinue treatment.

Results

A total of 80 patients were treated by the above method. Importantly, most of them were either receiving compensation or were currently involved in litigation in compensation or negligence suits because of accidents. This is mentioned since the economic factors of extended illness might be considered important to these patients and all of them would gain secondarily by prolongation of their symptoms. The number of treatments varied from 2 to 55 with a median of 18 treatments (Table I).

TABLE I

Number of CO_2 Treatments

1-10	11-20	21-30	31-40	41-50	51-60
17	32	15	7	7	2

Some patients recovered in three weeks and a few required as much as four months to recover. In the latter group, it was noted that these patients were basically neurotic or passive dependent characters as brought out by psychiatric examination and psychological testing.

Overall quantitative evaluation of the therapeutic effects of carbon dioxide inhalations showed that of the 80 patients (Group C, Table II) 57 made a complete recovery, 11 showed improvement, 11 discontinued treatment and only one patient was unimproved. This results in a complete recovery rate of 71% (Table II) or, of those taking the treatment fully, 80% recovered, 98% improved.

TABLE II

Results of CO_2 Treatments

Group	N	Median Number of Treatments	Recovered	Improved	Unimproved	Recovery Rate	Improved Rate
A	46	19	33	13	0	71%	100%
B	34	16	24	9	1	70%	99%
C	80	18	57	22	1	71%	98%

Of the 11 patients who discontinued therapy all showed some improvement.

Consideration was given to the effectiveness of treatment in terms of the duration of symptoms. Forty-six of the 80 patients had been suffering from post concussion syndrome for less than six months before beginning CO_2 inhalations. In this group (Group A), after a median number of 19 treatments, 33 patients made a complete recovery and were asymptomatic when discharged and 13 were improved. The complete recovery rate was 71% (Table II).

Of the 80 patients 34 had been suffering from the effects of their injury for 6 months to 50 months. They had been treated under various regimes without apparent amelioration of their symptoms. It is significant that of these 34 patients, with their long standing symptomatology, 24 recovered completely, 9 improved and only one showed no improvement. With this group a median number of 16 treatments was administered. Since this group of patients had been ill six months or longer, they might be considered as a control group for they had not responded to other forms of treatment. They showed a recovery rate of 70% which compares favorably with the recovery rate of 71% for the group as a whole and with the recovery rate of 71% for the group which had been ill for a period of less than six months (Table II).

Improvement was initially noted by a decrease in the intensity and frequency of headache followed by a decrease in nervousness and irritability. In view of the fact that almost all of these patients could gain economically by prolongation of their symptoms, the criterion of recovery, much less improvement, is particularly significant.

Discussion

It is felt that the carbon dioxide-oxygen inhalations were effective because the increased CO_2 tension reduced the irritability of presumably damaged nerve cells, increased the oxygen tension, and increased cerebral blood flow. These factors could lead to healing and correction of the underlying dysfunction (Courville). Whatever beneficial effects accrue from transient increased arterial O_2 tension might also be considered.

These beneficial effects are in conformity with the concepts of the neuropathology of the post concussion syndrome wherein there is damage and irritability to nerve cells, focal ischemia due to vasospasm and vasomotor instability. Consideration should be given to the notion held by some that this syndrome is really a neurosis and may be benefited by CO_2 as other neuroses are.[13] Such a tenet has been disproved by Courville and Rand, and certainly the rate of improvement is significantly greater than that claimed in the treatment of anxiety neuroses. A present study is under way correlating the response to treatment with the amount of neurotic signs as shown in the clinical examination and Rorschach testing. This study will also consider the incidence of post concussion syndrome following head injuries in relation to neuroticism.

Summary

Eighty patients, all suffering from post concussion syndrome were treated by carbon dioxide-oxygen inhalations. Following a median number of 18 treatments: 57 patients made a complete recovery in that they were asymptomatic; 11 showed improvement; only one was unimproved. A complete recovery rate of 71% was obtained with an improvement rate of 98%.

It was presumed that histologic and cellular changes occurred in either the cerebral cortex or nuclear masses of the brain stem, or in both, in brain concussion. These changes resulted in the subjective complaints known as post concussion syndrome.

It was hypothesized that the carbon dioxide-oxygen inhalations decreased the irritability of the presumably damaged nerve cells by increasing the CO_2 tension, increas-

ing the O_2 tension and increasing the cerebral blood flow. Presumably, correction of the underlying dysfunction and healing occurred.

It is suggested that this clinical report might provide a reference and stimulus point for further studies where more rigid experimental control could be obtained.

Miami, Florida.

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Some Pharmacologic Aspects of Indoklon, a New Pharmacoconvulsive Agent*

EDWARD B. TRUITT, JR., PH.D.,
ALFRED S. C. LING, M.S.,
ALBERT A. KURLAND, M.D., and
JOHN C. KRANTZ, JR., PH.D.

Indoklon (hexafluorodiethyl ether) is unusual among related fluorinated ethers in producing convulsions in many species of laboratory animals and man. It has many properties of practical importance in the application of its action to the treatment of mental disease. By the inhalation route of administration it exceeds other agents given by oral and intravenous routes in rapidity of action and control of dose level. The cessation of respiration during the tonic phase of the convulsion affords an automatic regulation of the dose required for effect. A period of preconvulsive unconsciousness in animals and man obliterates the feeling of extreme anxiety which preceded metrazol convulsions. A ratio of approximately 10:1 between convulsive and toxic doses in animals suggests that a wide margin of safety exists.

A film presentation was made of the related chemical formulae, the response of rats, dogs and monkeys to Indoklon, the evolution of inhalers for its application to man and scenes of the therapeutic use of Indoklon in mental patients.

The EEG response to Indoklon in anesthetized monkeys and dogs treated with muscle relaxant drugs appears to resemble the spike and slow wave typical of metrazol-induced convulsions. Chronic treatment of rats and dogs with Indoklon on a schedule similar to the usual regimen for ECT produced no lesions or biochemistry changes attributable to the drug.

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DISCUSSION

LOTHAR B. KALINOWSKY, M.D.

I had the opportunity to observe a group of patients treated with Indoklon at the Spring Grove State Hospital.

It is, of course, too early to say whether the Indoklon convulsion will have lower incidence of fractures than ECT. That is the decisive point. There is reason to believe that Indoklon does have greater safety in use. In the metrazol treatment the patient starts out with what has been called "a first clonic phase," but it is actually a more irregular irritative phenomenon due probably to cortical stimulation. This is followed by the usual clonic and tonic phase of the convulsion. However, the patient is already in deep unconsciousness when he goes into the tonic phase and, therefore, as in convulsions developing in insulin coma, he goes more slowly into the convulsion. In the metrazol convulsion there is a sudden onset of the tonic phase in spite of the preceding muscular contraction, and therefore it is more apt to lead to fractures. Since I have always been convinced that electricity as such has no therapeutic effect, and furthermore probably adds to the post-convulsive memory impairment, Indoklon could easily replace ECT.

This presentation demonstrates the constructive work of the pharmacologists in preparing this new inhalant for the use of the psychiatrists.

Moderator's Closing Remarks

LAWRENCE H. GAHAGAN, M.D., PH.D.

I should like to comment briefly on the excellent papers presented at this Round-Table Discussion on Experimental Investigations.

Doctor Gilbert's findings on the beneficial effect of carbon dioxide inhalation in the treatment of the post-traumatic syndrome, if substantiated by other investigators, will be a major advance in psychiatric treatment. It can be fairly stated, I believe, that carbon dioxide inhalation therapy, despite its sound theoretical basis, is generally disappointing in results. This is surprising since carbon dioxide is perhaps the most effective cerebral vasodilator. Parenthetically, papaverine by mouth is an effective vasodilator and it is much easier and safer to administer than carbon dioxide. So far as I know, its value has not, however, been established for any psychiatric condition.

Doctors Ellis' and Colville's paper on the differential arterial blood pressure responses to transcranial electric stimuli of graded intensities is a contribution in basic neurophysiology. Their technic is an original means for separating the sympathetic and parasympathetic components of the autonomic response to transcranial stimulation. In ECT, as usually administered, the stimulus is supramaximal. In these animal experiments, graded submaximal as well as supramaximal stimuli are administered. Their method is akin to that of physiologic dissection.

The paper by Doctors Truitt, Ling, Kurland and Krantz on the new pharmacoconvulsive agent, hexafluorodiethyl ether (Indoklon), is exciting and may well introduce a new means for carrying out convulsive therapy. The high effectiveness of electroconvulsive therapy is not dependent upon any property of electric stimulation per se. There is, for example, no doubt concerning the effectiveness of metrazol-induced convulsions.

The replacement of metrazol by electroconvulsive therapy was merely an expedient convenience. In my opinion, it is unlikely that modified electroconvulsive therapy will be soon replaced unless it is clearly demonstrated that Indoklon inhalation is easier and safer to administer and as effective as modified ECT.

Unlike several of my colleagues, I have not found iproniazid or the other "antidepressant" drugs of much value. In the treatment of depression, I would say that Ritalin, for example, has about the same efficacy as a cup of black coffee.

New York, N. Y.

4. Value of Non-Convulsive Technics

Non-Convulsive Technics

BRIAN C. CAMPDEN-MAIN, M.D.
Moderator

Introductory Remarks

At this Round-Table we will discuss the indications for non-convulsive electrical treatment. Perhaps it would be well to bear in mind not only the indications as we see them now, but also to give some thought to the directions in which future progress might be made. In order to provide a background for such a discussion, I have, as moderator, decided to open the Round-Table by giving a brief historical background of non-convulsive treatments as these are known to me.

In 1903 Babinski treated patients with non-convulsive electrical stimulation. He appears to have been the first physician to use this form of therapy. In 1939 Berkwitz found that high frequency faradic currents administered without loss of consciousness were effective in removing fear and excitement. He also reported favorable results in depression, hysteria, schizophrenics, and organics. He noticed that, "when during subsequent administrations of an intravenous barbiturate, respirations became irregular, a few additional faradic shocks quickly revived the patient."

In 1942 Delmas-Marsalet, using direct current, categorized responses into (1) minor seizures, or "absences without apnea," (2) "absences with apnea," and (3) "absences with muscular contractions, but without grand mal." He reported that these forms of treatment were effective in hypochondriacal depression and in calming the manic; otherwise, he found the treatments inferior to grand mal. He maintained that, for treatment to be effective, the patient must lose consciousness.

In 1944 Gottesfeld reported that non-convulsive stimulation was not an effective form of treatment; and, in 1946, Kalinowsky and Hoch reported that it was ineffective in the treatment of psychotics.

In 1948 Leo Alexander introduced the concept of "Countershock," which he found relieved the respiratory and circulatory side effects of E.C.T. He also found that it removed post-treatment anxiety, restored memory defects, and that it was a valuable adjunct to psychotherapy in anxiety neurotics; he maintained that countershock loosened the patient's defenses. He stated, "It is important that this treatment always be given in association with ventilative and interpretive psychotherapy." Subsequently, Alexander reported that the non-convulsive treatment altered the patient's response pattern to autonomic stimulation. In the Funkenstein Test, there would be a reduction in epinephrine-precipitable anxiety with prolongation of the blood pressure fall after the injection of Mecholyl.

In 1949 Hirschfeld independently corroborated the findings of Delmas-Marsalet and, like Alexander, emphasized the efficacy of non-convulsive stimulation in the treatment of patients with anxiety.

Around 1950, various investigators, notably Banay, Friedman, and Wilcox independently introduced various techniques of non-convulsive electro-sleep. It was found that these forms of treatment could be especially effective in the treatment of the paranoid schizophrenic. Wilcox claimed that, when treatment was started with a convulsion (as in the electronarcosis techniques developed by Tietz), the clinical effect was different from that of electro-sleep initiated by relatively high non-convulsive currents.

In 1952 Berkwitz, using low faradic electro-stimulation of the non-convulsive type, treated a group of patients with Pentothal alone, and then later added non-convulsive stimulation. He found "significant improvement did not occur until electrical stimulation was added."

In 1953 Hargrove treated a group of patients with anxiety and depression, giving them non-convulsive electrical stimulation, along with psychotherapy, and found that these patients did less well than a group treated with psychotherapy alone. In 1955 Montague and Davis treated 50 patients with non-convulsive electrical stimulation and found no significant difference from 50 patients in a control group.

In 1954 Hawkins and Robie reported on the efficacy of electrical stimulation in the treatment of barbiturate coma.

In 1955 Epstein introduced the technique of Monopolar Non-Convulsive Electrical Stimulation. A modification of this technique, Monopolar Deep Sleep, has been found by Epstein and Campden-Main to be effective in the treatment of those "hard-core" cases which have failed to respond to other forms of electrical therapy.

During the last year, reports have appeared concerning the facilitation of psychotherapy by ultrahigh-frequency alternating currents delivered through the Sedac attachment to the Reiter electro-stimulator. (The Sedac attachment is a filter which reduces the painful components of the Reiter convulsive currents.)

Value of Non-Convulsive Technics

PAUL H. WILCOX, M.D.

Non-convulsive electrostimulation (ESnc) of the brain is a distinctly different treatment from electroconvulsive treatment (ECT). Focal or unilateral electroconvulsive treatments more closely resemble ESnc than ECT. The EEG reverts to the pretreatment pattern within seconds after the cessation of the stimulation in ESnc and also after the cessation of the motor reactions in focal and unilateral convulsions. Only when the central excitatory process crosses the midline and produces a generalized bilateral tonic-clonic seizure is the EEG changed in the characteristic post-convulsive pattern. I believe I am correct in stating that these were the findings in some patients studied by Impastato. Whenever a generalized convulsion is introduced, even though followed by low electrostimulation, the EEG pattern is changed and it has the distinct features of a convulsive treatment.

My observations indicate that there are depressions which respond better to ESnc than to ECT and conversely that there are depressions that respond better to ECT than ESnc. Those who report good results in depressions with focal or unilateral convulsions should test out those patients with ESnc and I predict that they will find that those patients will do as well without the convulsions. On the other hand, the patients who fail on ESnc will likewise fail on focal or unilateral convulsions, but may respond to generalized convulsions. I arbitrarily classify the depressions which respond better to ESnc as reactive depressions and those which respond better to ECT as endogenous depressions.

I don't know whether "monopolar" electrostimulation or pharyngeal (nasal electrode) electrostimulation warrants any different conclusions regarding ESnc and ECT.

Emerick Friedman has been using various electrode positions for non-convulsive electrostimulation as well as for ECT and for ECT followed by low electrostimulation since 1941. He has come to some definite impressions as to special therapeutic indications for certain electrode positions and treatment patterns which I'd like to hear him say more about.

Traverse City, Michigan.

Non-Convulsive Diencephatic Electrostimulation

CARL BREITNER, M.D.

The title of this Round-Table Discussion would seem to indicate that there may be a question whether non-convulsive electric treatment techniques are useful. The excellent papers and demonstrations presented during this meeting and the privately expressed opinions by members of this group leave little doubt that convulsive therapies have a definite place in our therapeutic armamentarium.

Non-convulsive therapy has been practiced at the Arizona State Hospital for several years and reports indicate that non-convulsive techniques have produced good results. We have been using a special technique employing a naso-pharyngeal electrode which permits higher current concentrations in the diencephalon. Experience with several hundred patients has led us to distinguish between this primarily diencephalic stimulation and the primarily cortical stimulation which occurs with the use of conventional

temporal electrodes. Both diencephalic and cortical stimulation can be administered non-convulsively or convulsively, depending upon the intensity of the current used and the tolerance threshold of the individual. Experience seems to indicate that neurotic anxiety states, as well as manic psychoses, usually respond to a small number of diencephalic stimulations with currents from 1 to 4 ma. Paranoid conditions, including schizophrenic as well as involutional psychoses, respond better to diencephalic stimulation using higher currents up to 10 or 15 ma. In this treatment, convulsive seizures may occur, but it should be kept in mind that these seizures have no side effects such as confusion or memory loss and that the electroencephalogram remained normal. If such seizures occur, they do not constitute physical hazards because they are induced gradually and with little clonic activity. Generally, it seems that those conditions which show the least favorable outlook with electroconvulsive therapy respond best to diencephalic stimulation and the psychiatric effects frequently included improvement in the patient's insight. The abreactive psychotherapeutic value of non-convulsive therapy, which was so well demonstrated by Dr. Wilcox, should also be considered. However, a special effort has been made lately to eliminate concomitant psychotherapy in a number of cases in order to evaluate the effects of the stimulation *per se* and the results remain favorable, indicating the specificity of the treatment. True depressive reactions respond better to cortical stimulation, as administered in conventional electroconvulsive therapy.

It may be worthwhile mentioning here that in depressive states we do differentiate between those cases which Drs. Alexander and Wilcox have labeled "endogenous depressions" with marked retardation, true suicidal attempts, deep feelings of worthlessness, hopelessness and guilt, and those depressions which are associated with marked overt anxiety, dissatisfaction with one's fate, fault finding and complaints, dissatisfaction with others, attention attracting suicidal attempts or suicidal threats, agitated crying spells, etc. The latter respond to diencephalic stimulation with low currents while the "endogenous depressions" become aggravated by such therapy and electroconvulsive therapy seems to remain the treatment of choice. In a number of schizophrenic reactions, including old chronic cases, improvement has been achieved by combining the diencephalic and cortical approach.

We consider ourselves as treating symptoms rather than a specific disease entity and we quite frequently change treatment techniques in a patient if the symptomatology changes during a course of treatment.

Phoenix, Ariz.

Multipolar Electrocoma Therapy

EMERICK FRIEDMAN, M.D.

Subconvulsive electrotherapies were employed extensively in the Metropolitan State Hospital and Norwich State Hospital from 1938 to 1947. Some of the work was done in association with Paul Wilcox and some by each of us working independently. Electrotherapy developed as a more or less natural outcome of the then general use of chemically-induced convulsive states. At this point it must be noted that all modalities of neurovegetative responses to electrotherapy reported through the literature had been accomplished by one or other form of chemotherapy; e.g., convulsive, akinetic, tonic and myoclonic reactions together with autonomic changes had all been described. Intense abreactions had been noted by me in the use of camphor therapy. Chronic psychotic patients would frequently emerge and revert to symptoms and signs that were presented at the onset of illness years before. Dynamic verbalization significant for psychotherapy were also reported. Chemotherapy was interrupted when it became apparent that modalities of electrostimulation would duplicate these reactions without the imposition of an added pharmacologic burden, which might include toxicity.

AC techniques were found to deliver supramaximal doses of current and permitted little flexibility for further experimental work, particularly with reference to the determination of threshold, sub-threshold and

localization values. To correct this unidirectional electrostimulation apparatuses and techniques were designed by Wilcox, Reiter and the author.

In our search for threshold convulsive levels, many combinations of unidirectional wave forms and electrode placements were applied until the unilateral temple-vertex placement was found to be the most efficient with fairly simple pulsating wave forms. In the course of this investigation, lateralizing signs were recorded, such as monoplegic or hemiplegic convulsive movements, torsions, laterotonus, localized myoclonus and autonomic responses with and without abreactions. To some extent these neurologic patterns could be induced with experience and skill. Thus, the various components of the convulsion could be evaluated with the eventual possibility of directional or localizing electrostimulation.

In consideration of possible electrode placements, there were reports of electroencephalograph work with intranasal and otic leads as well as preelectroencephalograph stimulation through the same electrodes, using faradic or relatively minute currents as purely investigative stimulation rather than therapeutic process. Many trials with pharyngeal and nasopharyngeal electrodes were undertaken with chronic patients. At first, a definite, satisfactory routine was difficult because the work was done without anesthesia. In many instances abreactions and reactivation of early psychotic symptoms were induced, which, when followed by standard convulsive treatment, brought about clinical improvements.

When treatments were administered with the aid of I.V. anesthesia, it was then possible to increase the intensity and duration of non-convulsive applications to the point of bringing out the neurologic vegetative signs found in chemotherapies. In my work three forms of application of non-convulsive procedure developed and could be routinely used in hospitalized and ambulatory office patients. This work is reported in the E.P. R.A. proceedings dated May 2, 1954, under the general heading of Multipolar Electrocoma Therapy. The first form, with nasopharyngeal-bioccipital leads, directed the current through the midbrain structures and, with relatively little motor response, produced powerful abreactions, rage, fearfulness and eroticisms with pressurized verbalizations of dynamic material.

The directions of usefulness of this modality were (a) to reactivate or disrupt a stable or encapsulated psychotic process into a more acute syndrome and then to treat with standard or four lead treatments (q.v.), (b) to bring about a more rapid change in cases showing severe anorexia, cachexia, neurasthenia. Successful results were achieved and reported in a preliminary manner. Follow-up results will be reported.

The second modality worked out was the fronto-(ethmoido)-bioccipital, three-lead electrocoma. Its usefulness was in cases of morbid, disabling, phobic-anxiety symptoms and in various types of addictions. The motor responses were of a rapid, general myoclonic type synchronous with the current peaks on the ammeter when the ethmoid lead was the positive pole. Similar but much less intense abreactions were noted as compared with the previously described procedure.

The third modality was the bioccipital-biparietal, four-lead electrocoma. It was found to be most useful in (a) acute psychoses whether of affective or schizo-affective type, (b) in paranoid psychoses, (c) in those cases which had been "reactivated" by the previous modalities and have assumed the picture of an acute psychotic reaction. The motor pattern is chiefly a continuous general rigidity with a superimposed myoclonus. An overall calming effect rather than any abreaction was an immediate finding.

It should be emphasized that the multipolar modalities for inducing electrocoma extend the range of usefulness of electrotherapy, that they may be interposed in the course of standard ECT and insulin therapies as an adjunctive or accelerative procedure, that they may be used exclusively in the respective conditions noted. A flexible treatment program may readily be set up for cases showing an admixture of disabling symptoms or cases showing changing symptoms. For example, an acute psychotic patient with marked overactivity would be given four-lead electrocoma for 3-4 succes-

sive days; he may present then marked apprehension and fearfulness. The modality may then be changed to 3-4 days of three-lead, fronto-bioccipital type. If depression is then marked, 3-4 standard ECT may be administered. Another example is that of disabling phobic anxiety; treatments would start with three-lead fronto-bioccipital and if depression supervenes, 1-2 standard ECT's are given, reverting then to the three-lead type. If an acute panic situation occurs, then several treatments with four-lead modality is given. Finally, the multipolar modalities of electrocoma have been readily and usefully adopted for maintenance therapy on an ambulatory basis.

Albany, N. Y.

Electrocoma Treatment by the Monopolar Method

JOSEPH EPSTEIN, M.D., and
BRIAN C. CAMPDEN-MAIN, M.D.

The monopolar method of electrocerebral stimulation was introduced by one of us several years ago.[1] Later on, we also introduced the monopolar method of inducing convulsions and described its rationale.[2] The advantage of the monopolar treatment is that its method of administration permits controlled selectivity of current. By holding the active monopolar electrode between his fingers (like a pencil), the operator is able to direct the current throughout the medulla, from the point at which the current enters to the selected point of application of the monopolar electrode. Our thesis is that the important areas to stimulate are the reticular activating substance and the thalamic nuclei. These areas are directly stimulated when the current is led through the brain in a sagittal or parasagittal direction. This is ideally accomplished by the monopolar method, utilizing one cuff electrode, which remains stationary and one electrode (the monopole), which is manipulated by the operator.

The technique by means of which we induce electric sleep has been described by us in other papers.[3,4] The electric sleep is induced by the monopolar method, and the current passes through the sagittal and parasagittal structures. In our original work, we induced the electric sleep without any previous intravenous sedation. We did this to insure that the electric current per se could induce narcosis. This fact is self-evident, and we now routinely induce light narcosis by intravenous thiopenthal (Pentothal). We also routinely administer 1/25 gr. atropine sulphate under the tongue one half hour before treatment. After the patient has been sedated, the cuff electrode is put in position on the right forearm, and a monopolar convulsion is induced. After about 40 seconds, when respiration returns, the procedure for the induction of electric sleep commences. Using the Reiter RC47D apparatus, the modulation knob is turned to about "twelve o'clock," and the ratio control knob is turned all the way to the right. The current is then increased to the maximum that will allow him to breathe, and then "bursts" of current are delivered by depressing the red button. The intensity of these bursts should be high enough to cause clonic movements of all extremities, but remain below the convulsive level. If releasing the red button does not permit free breathing, then the active monopole is lifted dropping current value momentarily to zero) and respiration returns. The duration of time that the red button is depressed is generally 2 to 4 seconds or the time required to cause 6 to 8 clonic movements. Releasing the red button reduces the current, eliminates the clonic movements and allows respiration to resume. During this process, the active electrode is applied to the vertex of the head. Every one-fourth minute, its position is shifted slightly to the right or left of the mid-sagittal line near the vertex. The center of the electrode need at no time be further removed than one inch from the midline. For the duration of the treatment, either the operator who administers the current or an assistant keeps a constant check on the rate and quality of her heart beats. The heart rate generally increases to between 140-170 per minute for the first minute, and then levels off to about 120. Any sudden slowing of the heart or any irregularity or weakness is indication to discontinue treatment. Treatment is generally terminated in six to ten minutes. The last minute of the treatment is devoted to adminis-

tering what we choose to call a "Spray." We now remove the monopole from the region of the vertex and slowly pass it across the forehead in front of one ear across to the other ear, just below the hair line. Thus, in addition to the sagittal stimulation, which we feel is the basis of the efficacy of electric-sleep treatment, the patient receives a cerebral spray type of stimulation in the shape of a V with its apex at the medulla and the base is the bitemporal-frontal region. The "Spray" at the termination of the treatment seems to be conducive to a smoother transition for the patient from the sleep state to the wakeful one.

As far as our results go, we continue to get more rapid recoveries and remission in about 12 per cent of hard core cases that have failed to improve from other methods.

New York, N. Y.

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Succinylcholine Technics: A Symposium

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Technic of Complete Myoneural Blockade in Psychiatric Electrotherapy

LAWRENCE H. GAHAGAN, M.D., PH.D., and D. JEANNE RICHARDSON, M.D.

The technic of complete myoneural blockade is designed for maximal safety in treatment and requires a basic team of psychiatrist and anesthesiologist. A cardiologist is added to this team whenever electrocardiographic observations are made during treatment.

Our aim is to avoid, or at least minimize, cardiovascular, musculoskeletal and respiratory complications in treatment. We have never refused treatment because of co-existing disease. We have, for example, successfully treated patients with aortic aneurysm, Adams-Stokes syndrome, advanced coronary sclerosis, unhealed fracture, unhealed surgical wound of the abdomen, bronchiectasis, etc.

Method: Our usual method of treatment, including continuous electrocardiography, is outlined in Table I. A more detailed description of this technic is reported elsewhere.[1] We shall mention here only matters of dosage.

Thiamylal (surital) sodium is most commonly used; the average dose is 400 mg. The intravenous atropine dose is now 2.4 mg. (1/25 grain); this will completely block the cardiac portion of the vagus nerve.[2] An atropine dose one-half this size, however, is usually sufficient.[3] The average dose of succinylcholine chloride (Anectine) ranges from 60 to 80 mg. The largest dose of succinylcholine was 140 mg. (The period of apnea averages 5 minutes and ranged from 1½ to 17½ minutes.)

Results: 413 treatments have been administered successfully to 36 patients, using this technic. Musculoskeletal complications are uniformly prevented. Cardiovascular stress is lessened. The prolonged period of apnea, averaging five minutes, is a predictable complication of treatment and is readily managed by the anesthesiologist, who administers 100 per cent oxygen by bag and mask. It is emphasized that the anesthesiologist is an indispensable member of the treatment team.

In a few cases tetraethyl ammonium chloride, administered intravenously about five minutes before application of the electric stimulus, is used experimentally in order to reduce the paroxysmal rise in arterial blood, which uniformly follows stimulation.[4] This ganglionic blocking drug, so administered, reduces the pressor response to approximately one-half its usual magnitude. Further studies of ganglionic and adrenergic blocking agents in transcranial electric stimulation are in progress.

From Doctors Hospital, New York City.

New York, N. Y.

TABLE I

1. Pretreatment sedation and other medications, e.g., digitalis, quinidine, antimicrobials, etc., are given as required. Patient is fasted for 3 hours before start of treatment.
2. Continuous electrocardiography (except during electric stimulation). Frequent recording of arterial blood pressure.
3. Intravenous barbiturate drip.
4. Intravenous atropine sulfate.
5. Intravenous succinylcholine chloride.
6. Control of respiration with 100% oxygen by bag and mask.
7. Electrostimulation (conventional technic).

Authors' Note: Dr. William Hall Lewis, Jr., and Dr. Daniel Sheehan, made the electrocardiographic observations in the foregoing study.

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Succinylcholine Chloride and Thiopental Preparatory to Electroconvulsive Therapy

IRVING E. GILBERT, M.D., SAMUEL E. WHITE, M.D., and LEO ALEXANDER, M.D.

Technique of Administration

When electroconvulsive treatment under thiopental (pentothal) anesthesia and relaxation by succinylcholine (anectine) is to be administered, the patient should be fasted for at least four hours before treatment. Our technique is as follows: an intravenous injection of 0.9 mg. (1/75 grain) of atropine is followed by 0.4 or 0.5 percent thiopental by rapid intravenous drip. When the patient no longer responds to oral questioning, and the lid reflex is just about abolished, i.e., at a light stage of narcosis, 20 to 80 mg., usually about 40 to 50 mg. of succinylcholine is administered during the following 10 to 15 seconds through the rubber sleeve of the intravenous tubing close to the needle, and the thiopental flow is then discontinued. As soon as the succinylcholine injection is completed, 100 per cent oxygen is administered by a face mask and rubber rebreathing bag connected to an oxygen tank. Within 10 to 35 seconds after the succinylcholine injection, the patient undergoes a series of generalized muscular twitching which subside within 5 to 10 seconds. These indicate that the depolarizing effect of the relaxant has taken place. Within 45 to 60 seconds after the succinylcholine injection, the patient undergoes a marked paralysis of the skeletal musculature of the body with concomitant apnea. As the patient goes into apnea, positive pressure oxygen is applied by the anesthesiologist, by squeezing on the bag 15 to 20 times per minute, to inflate the lungs in simulation of normal respiration. With our technic the flaccid paralysis of the skeletal musculature reaches its height 65 to 70 seconds after the succinylcholine injection, and this is the best time to initiate the shock current desired. The patient undergoes a vestigial type of convulsion, usually limited to the upper facial musculature and the toes and metatarsals of the feet. All movements of the spine and chest wall, usually also of the arms, are eliminated, and the glottis remains open, thus preventing the Valsalva phenomenon, as well as fractures. We have found it unnecessary to introduce a bite block, or to use an oropharyngeal airway routinely, although the latter should be available when necessary to maintain a patent airway, especially in patients with short, thick necks. The advantage of not using them routinely is that they tend to increase salivation, and the oropharyngeal airway may set off laryngospasm in predisposed individuals. Administration of oxygen under positive pressure is continued throughout the treatment and for the following few minutes (usually 2-4 minutes), until completely normal spontaneous respiration has been resumed. Thus, all anoxia can be prevented throughout the treatment and the patient's complexion kept at a healthy pink color throughout all phases of the seizure. The advantage of steady maintenance of oxygen supply to all tissues, especially in elderly and arteriosclerotic patients cannot be estimated too highly, and constitutes one of the greatest advantages of this type of treatment.

At termination of treatment, once the patient is breathing naturally and adequately, he is placed on his side so that the tongue does not obstruct the normal flow of air during respiration. Should mucus or vomitus appear at this phase, it will then drip out of the side of the mouth, instead of being aspirated into the trachea and lungs. The patient should be carefully watched during the post-treatment period, and should oral or pharyngeal mucus obstruct the air passages this is aspirated through a catheter by means of a suction machine which must be available at all times.

Laryngospasm is a rare complication, but the therapeutic team must be prepared to treat it promptly. The treatment consists in prompt administration of oxygen under

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positive pressure, and unless the obstruction yields immediately to the positive pressure by means of manual compression of the bag, an endotracheal tube must be promptly inserted. If necessary, this can be facilitated by giving more succinylcholine intravenously. This is another point in favor of having two physicians participating in the administration of the treatment. In skilled hands, the insertion of the laryngoscope and passage of the endotracheal tube, can usually be accomplished in ten seconds. It may be a life-saving measure.

In our 4,783 treatments in 388 patients, we have found endotracheal intubation necessary in only one patient, who responded promptly to the measure.

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Greater Safety by Softer Electroconvulsive Treatment with SCC and Neraval

THEODORE R. ROBIE, M.D.

Electroconvulsive therapy is still the most reliable method of treating the acute suicidal, depressed patient. Chemotherapy including iproniazid does not bring about as quick a recovery from the suicidal urge as electric therapy. Electroconvulsive therapy is also one of the best methods we have for treating schizophrenia, particularly when repetitive maintenance therapy is necessary.

In every patient being given the first electroconvulsive treatment the test of susceptibility to succinylcholine (SCC) is carried out. The patient is administered a standard dose of 5 mg. intravenously and the reaction is awaited. In 30 seconds or less the patient will begin to scowl somewhat and oftentimes an expression of wild agony will show itself, while the patient either states that he cannot breathe or that he is having difficulty in breathing and on some occasions he is unable to speak. He will also state that he is feeling electrical sensations or twitchings in his neck and throat and extending down through other parts of the body in some instances. While looking at the shoulder or neck muscles one can often see muscle fasciculations. Soon partial limp paralysis is evident in arms, but in less than two minutes as a rule, the patient will begin to show relaxation in his expression and will admit that the unpleasant sensations are wearing off and in two full minutes (in practically all cases) the prostration effects have disappeared.

Based on this test and the degree of reaction which the patient shows, the dosage of SCC is then estimated in accordance with the degree of prostration effects. The estimate is made in the following manner: if there is very severe prostration the dosage decided upon is between 20 and 24 mgs. —if moderately severe then the dosage is usually between 26 and 30 mgs. and if very mild effects are observed the dosage is between 30 and 36 mgs. depending upon the weight of the individual. If you are dealing with a very heavy person then the dosage is a bit higher, maybe 38 or rarely even 40 mgs. After the first treatment has been given a notation is made as to the degree of paralysis induced while the convulsion was occurring and thereafter the dosage of SCC is then raised or lowered in accordance with the effect observed. Dosage will also be influenced by the period of apnea following the first treatment.

With Neraval the dosage is usually between 300 and 350 mgs. for the first treatments. About one fiftieth gr., or 3 cc. of atropine is given in the same syringe with the Neraval. We use the 2.5 per cent solution of Neraval which keeps the coughing reflex at a minimum. We have rarely observed coughing but others have reported it. When the anesthetic is administered it is given in a 20 cc. syringe which allows adequate space for both the Neraval and the atropine. The Neraval and atropine having been injected into the vein, one then waits at least 45 seconds. During that period usually the patient will yawn at between 25 and 30 seconds, and at 45 there is deep anesthesia if the dosage has been adequate. Immediately thereafter the SCC is injected and then a further delay of 60 seconds (1 minute) is allowed, in order to insure the full paralyzing effects of the SCC. Occasionally there will be short lived arm or leg movements if the Neraval-coma is not as deep as appeared. At this point the convulsion is induced.

While I am partial to the Reiter machine because of the advantage it has in giving electrostimulation immediately following the convulsion, other electrical apparatus is adequate in carrying out the convulsive treatment. The paralysis produced by the SCC will certainly protect the patient from fractures even with the stronger voltage machines. However, they do not have the advantage of the electrostimulatory facility following the treatment which is a real help in overcoming the respiratory arrest and in eliminating whatever barbiturate has been given as an anesthetic.

It is good policy to always record in each instance immediately following the treatment, the exact degree of paralysis observed as well as the degree of anesthesia. If there has not been a sufficient degree of anesthesia the patient is likely to complain when he returns for his next treatment and there may be difficulty in getting him to take additional treatments unless reassured his discomfiture can be prevented. The dosage of the anesthetic should be just enough. As for the degree of muscular paralysis it is exceedingly important to record whether it is 3 or 4 plus paralysis that you observe, in order that you may properly estimate the dosage of SCC to be given in the next treatment. It is also of some value to record the degree of salivation since you may wish to raise or lower the dose of atropine in accordance with your views of subsequent dosage. I have never seen any harm in giving the full one-fiftieth grain to all patients and some particularly heavy patients, namely those over 200 lbs. may require more to produce adequate decrease in salivation.

A technical maneuver that may have advantage, particularly in those showing prolonged apnea following SCC electroshock, is to oxygenate the patient during the 60 second delay while SCC is inducing its full paralyzing effects. This brings quicker respiratory response from the SCC induced prostration following the convulsion. However, too much oxygen may increase the overactivity some patients show during the recovery period.

East Orange, N. J.

PM-GM Succinylcholine Modified Electroshock Therapy

ANTHONY R. GABRIEL, M.D.

Psychiatrists have found succinylcholine (SCC) of tremendous aid in reducing the incidence of fractures in electroshock therapy (EST) by its effect of diminishing the violence of the convulsion.

As a muscle-relaxant, SCC produces its full effect in about 30 seconds following rapid intravenous administration. Within ten seconds the patient complains of dizziness, diplopia, throat pain, and is partially paralyzed and apneic. Waiting another 15 to 20 seconds to allow full muscular relaxation to develop before producing the convulsion will result in the remembrance of these extremely unpleasant sensations and the possibility of the patient's refusal of further treatment.

The concomitant use of an ultra-short acting barbiturate (USAB) usually resolves the SCC anxiety problem but leads to prolongation of the apnea. Barbiturates are strong central respiratory depressants capable of producing severe reactions, including death, even in small doses.

Therefore, the utilization of small doses of SCC without barbiturates is desirable. By rendering the patient unconscious with a petit mal stimulation soon after the SCC injection, it is possible to eliminate the recall of the feeling of suffocation and fear. This in essence is the "PM-GM" succinylcholine-modification of electroshock therapy. The actual PM-GM technic is as follows:

Selection and preparation of the patient for EST is made in the usual manner. One-half hour prior to the treatment 1/50 grain (1.2 mg.) of atropine is given either intramuscularly or sublingually. If this is not feasible, the atropine may be given intravenously from a separate syringe just before the SCC injection. Ten mg. of SCC is then given rapidly intravenously using a tuberculin syringe and a 26 gauge hypodermic needle. When fibrillations are noted about the patient's mouth or when he shows signs of impaired breathing (within 5 to 10 seconds after the injection) the petit mal stimulation is given. The patient may react to the petit mal by raising his hands toward the electrodes or muttering a word or two, which is not recalled after the grand mal treatment. The patient now remains motionless and without breathing. Ten to 15 seconds after the petit mal, the grand mal stimulation is given in the usual manner. Adequate relaxation occurs in practically all patients. If more relaxation is needed a few more milligrams of SCC may be given on the next treatment. The convulsion proceeds in the usual manner of SCC—modified convulsions. Invariably the patient is breathing by the end of the convulsion or will begin to breathe within a few seconds, eliminating the need for oxygen. Following the convulsion the patient recovers quickly since he has not received barbiturates. He is usually confused and denies having had a treatment. Later, when clearer, he may remember he had a treatment but the only thing recalled clearly is the injection.

The PM-GM technic may be given with any shock machine. It is important to have the petit mal strong enough to produce complete unconsciousness in order to prevent recall of the unpleasant sensations of both the SCC and the petit mal which would lead to fear of the treatment. When the PM causes a convulsion, the electric dosage can be lowered at the next treatment to avoid the convulsion.

When the Reiter AC instrument, Model MCL-AC II, is employed, the current selective switch is in "Medium" position: for the petit mal stimulation, the treatment button is pressed and released immediately; for the grand mal stimulation the treatment button is pressed for 3 seconds. (With the ordinary Cerletti-Bini AC apparatus a setting of 110 volts for 1/10 of a second will produce an adequate petit mal in most patients.) With the Reiter unidirectional current machines, two technics may be used: For the petit mal the machine is pre-set at the full range, that is, 20 ma., 10 mg. of SCC is given and five to ten seconds later the treatment switch is quickly turned on and off. Ten to 15 seconds later, the GM is given beginning at 15 ma. and increasing to 20 ma. within a few seconds, and proceeding in the usual

manner. In the second technic, the machine is set at 15 ma.; the SCC injection is given; five to ten seconds later, the current is turned on, keeping it steady at 15 ma. for five or more seconds, then gradually increasing within another five seconds to 20 ma. and then held there until the patient enters the tonic phase of the convulsion. Here no petit mal is actually given. In effect, however, the prolonged induction time, from the time the current is turned on until the patient enters the tonic phase, ten or more seconds, may be considered a fractionated long-lasting petit mal. Both methods are effective.

This procedure further simplifies and makes safer the administration of SCC, without barbiturates, and has demonstrated clearly that in EST only small doses of SCC are needed to produce the desired result. The advantages derived from the PM-GM succinylcholine modified EST are: complete amnesia; no anxiety; full muscular relaxation; earlier return of breathing with no apnea or at most apnea of very short duration—not requiring the administration of oxygen under pressure; need of less SCC—8 to 10 mg.

The indications for this technic are the same as those for other forms of succinylcholine—modified electroshock therapy.

New York, N. Y.

PM-GM Succinylcholine (SCC) Technic

JOHN M. ERDOS, M.D.

From November of 1956 to October of 1957 we used succinylcholine chloride (Anectine) as a muscle relaxant medication in ECT on 82 patients. Our techniques are those outlined by Dr. Gabriel and demonstrated at the October 11th meeting of the Eastern Psychiatric Research Association held at Kings Park State Hospital. Our dosage of Anectine was usually only 10 milligrams but on rare occasions was increased if the need was clinically observed. In such instances we increased dosage to 15 or 20 milligrams and in the early days we went as high as 25 milligrams. In our initial use of Anectine we would wait one half to one minute following administration of the muscle relaxant before administering the ECT, in order to achieve the maximum effect of the Anectine. We observed, as pointed out by Dr. Gabriel, that patients became restless during the waiting period, and after treatment would recall that they had experienced a sensation of suffocation. Indeed, at the next appointment, it was often difficult to persuade the patient to continue treatment. Thereafter we fully adopted Dr. Impastato's P.M.-G.M. technique as described in his article in the November 1956 issue of "Diseases of the Nervous System." Our patients were premedicated with 1/75 grain atropine sulphate injected subcutaneously about one half hour before treatment. At treatment time we quickly injected 10 milligrams Anectine I.V. and 10 seconds later gave a petit mal electrically in order to produce amnesia. This petit mal was applied in order to avoid the use of Pentothal and so that patients would not experience any suffocating sensations following Anectine administration. For the petit mal we set a Reiter Electrostimulator to about 20 milliamperes and applied the current quickly for a fraction of a second to provide the amnesic petit mal. When we used the Molac II instrument, the petit mal was accomplished by setting the instrument to a high position, pressing the button, and instantly releasing it. Twenty seconds after the initial petit mal we again pressed the button and held it to produce the grand mal. Prior to treatment an especially designed rubber mouth gag with a breathing hole was introduced into the patient's mouth through which patients would be able to breathe before, during and after treatment. Immediately after treatment, oxygen was administered routinely with a face mask until the first deep inspiration was noticed. On occasion we used the Reiter Electro-stim-

ulator with electrodes applied to the bifrontal area in order to force the patient to breathe. With the above techniques we found that patients were no longer fearful as before and came to the treatment room without objection. Only four patients in this series had post-convulsive excitement. Of these, one patient was somewhat quieted by administration of 200 milligrams of Sparine injected I.V. immediately after cessation of seizure. With this excitable patient we found that his low threshold required low electrical dosage for optimum treatment. We were able to avoid the excitement entirely with adequately low electrical dosage. We avoided overtreatment and thus prevented post shock excitement.

To assure complete safety, new patients were started on five milligrams Anectine and were given 10 milligrams on subsequent treatments only if the first treatment dosage was well tolerated. We found these dosages of Anectine produced adequate muscle relaxation, yet patients uniformly breathed within a few seconds after termination of treatment. In the few instances where the patient became cyanotic during treatment and we found it desirable to administer oxygen prior to treatment and thus avoid cyanosis. No clinical signs of fracture were found in any of the patients treated in the abovem anner.

I consider the above described petit mal-grand mal technique with the Reiter Electrostimulator or the Molac II in patients premedicated with small doses of Anectine a simple and safe technique. The advantages are:

1. The procedure has eliminated fractures.
2. Patients do not exhibit any violent muscle contractions, nor experience muscle pain or general weakness following treatment.
3. The petit mal insures elimination of anxiety with respect to treatment sensations.
4. Minimal assistance is required, an important desideratum in a state hospital where personnel shortages are to be considered.

The disadvantage of respiratory depressant action of Anectine is so greatly minimized with use of 10 milligrams as to be negligible. I prefer the unidirectional current Reiter Electrostimulator because I have found it possible to thoroughly and effectively stimulate patient respiration immediately after treatment whenever necessary.

I have used the crescendo or gradual rise technique with fine results. This method calls for the injection of the Anectine and the beginning of electrical treatment within ten seconds. The current is gradually raised from 15 milliamps of convulsive current to the end of the scale or until the patient experiences the grand mal seizure.

Succinylcholine Modified Electroconvulsive Treatment

WM. L. HOLT, JR., M.D.
Albany, New York

I have been asked to present a description of the method of succinylcholine administration I now employ at Albany Hospital. It is as follows:

The patient is treated on an empty stomach, 20 to 60 minutes after an intramuscular injection of 0.6 mgs. atropine sulphate. The treatment table is an ordinary four-wheel stretcher that will rotate 360 degrees, with wheel brakes on one end. The table length rubber pad is covered with a blanket and the stretcher so placed that the locked wheels are at the patient's head. Sodium pentothal solution in 5% strength is injected into a vein with a 5 cc. syringe and 20 gauge needle, in the space of a few seconds, the dose being that which will produce unconsciousness with loss of wink reflex—250 mgm. being sufficient in routine cases. The syringe needle is left in the vein and a syringe containing succinylcholine chloride (SCC) is attached to the needle while awaiting the onset of the Pentothal narcosis. When the depth of anesthesia is satisfactory, sufficient SCC is injected to produce the amount of muscle flaccidity desired, usually between 30 and 50 mgm. Sixty seconds are allowed to elapse between injection of SCC

and administration of the electroshock.

During this minute oxygen is administered to the patient by a positive pressure method through a closed system with a rebreathing bag. A rubber inflated face cushion and transparent face piece provide an air-tight fit for the mask with good visibility, a safety feature, should regurgitation of stomach contents occur.

Prior to administering the electric shock, the oxygen mask is removed and a rubber bite block inserted between the teeth. This time of insertion is chosen so that the examiner will be sure to test the degree of muscle relaxation at the jaw and may be alerted to the possible need for more SCC. This bite block does not interfere with the oxygen mask. It allows the insertion of a Guedel airway and use of suction into the posterior pharynx. Any standard electroshock machine may be employed for the electrical stimulus, and more than one such stimulus may be given before the effect of the drug is significantly lessened, the drug modification being effective for about three minutes. Upon conclusion of the seizure, further oxygen is not usually required. When patient's diaphragm is seen to resume spontaneous movement, the rubber bite block is removed and replaced by a Guedel airway. Flow of air through this airway is tested before the patient is placed on a low recovery bed out of view of the operator. Recovery beds are placed close together so that the patient cannot roll to the floor. An attendant nurse watches the patient's breathing and color and remains constantly present with the patient until consciousness fully returns, approximately ten minutes after the treatment.

With the technique described above our clinic has given approximately 30,000 treatments without anesthesia complications save for a rare dermatitis attributed to Pentothal.

Electro-Sleep Technics: A Symposium

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Electric Stimulation of the Diencephalon

CARL BREITNER, M.D.

Ever since the discovery that electrically induced convulsive seizures have a beneficial effect upon mental disorders, numerous modifications of ECT have been proposed and practiced. It would seem trite to add another suggestion, were it not for the fact that the vast majority of electrotherapeutic techniques have one thing in common: they stimulate primarily the cortical areas of the brain, and any effects on diencephalic areas are either indirect, coincidental or minor. Furthermore, the degree or duration of stimulation of the cortex has to be limited in order to avoid permanent damage. Therefore, in cortical therapy, the stimulation of the diencephalon is restricted.

Experimental evidence indicates that some mental diseases are associated with disturbances of diencephalic functions. The diencephalon is known to be a relay station for most autonomic functions, including sleep and awareness, rage and placidity, appetite, blood pressure, etc., all of which are factors related to behavior, emotional response and a normal thought content.

The original thought leading to the technic described in this paper was to find a way to increase the effect upon the hypothalamus, i.e., concentrating the electrical field in that area. Almost all technics of electrotherapy use elctrode application over the calvarium which stimulates primarily the cortex. Exceptions are — the monopolar method developed by Joseph Epstein,[1] and the reported use of a nasal electrode for ECT by Emerick Friedman.[2] Epstein claims better results than are obtained by conventional methods, for the reason that part of the current passes through the brain stem. It is reasonable to assume that his results, in cases where old technics have failed, may be ascribed to this fact. Friedman's reported case histories do not include non-convulsive treatments.

In this study, non-convulsive currents were used with minimal intensity. It is increasingly evident that there is an optimal amount of stimulation beyond which beneficial effects are obscured by ill effects such as increased anxiety, memory loss and confusion. On the other hand, the favorable results reported with electric coma or deep sleep therapy might be attributed to the fact that in these longer-lasting treatments the diencephalon is reached more effectively.

In the search for a method which would stimulate primarily the diencephalon, anatomical considerations led to the design of special nasopharyngeal electrodes and scalp electrodes. Originally only minimal currents were used, concentrating the electrical field in the diencephalon and minimal currents are still the treatment of choice in many disorders, including certain psychoses. Using currents up to 4 milliamps., results by this method varied. There were cases which responded dramatically to one to three treatments, and others which responded only to a greater number of treatments, similar to conventional ECT. Then there were those cases which showed no improvement with non-convulsive diencephalic stimulation. Extended observation seems to indicate that certain disorders benefit more from currents up to 15 milliamps. However, with additional experience we now select which type of treatment is most likely to succeed in each case.

Several important facts have emerged to date. 1) There is a difference between the effects of diencephalic and cortical stimulation, and we have at our disposal a choice between the two types. 2) Some disorders which in the past have shown the least favorable response to ECT have responded best to non-convulsive diencephalic stimulation. 3) It has been established that diencephalic stimulation, convulsive or non-convulsive, does not produce any change in the EEG, and it is not necessary to produce undesirable side-effects such as memory loss and confusion in order to improve the mental condition.

In the earlier stages of this work the main advantage of this type of therapy was seen in its lack of hazards or side effects. However, today we feel that in addition favorable

results can be obtained in cases previously resistive to other therapies.

Continued observation and use of the new type of therapy has provided indications as to which type of treatment would have the best chance to succeed. In cases in which anxiety and excitement are predominant features, the diencephalic approach has produced better results. Both neurotic anxiety states and manic psychoses usually respond quickly to diencephalic stimulation, with minimal currents. Paranoid conditions with delusions or hallucinations also respond well to diencephalic approach, using higher currents. A number of paranoid patients previously resistive to ECT have improved with diencephalic stimulation and have left the hospital. The majority have not returned over the observation period available. Depressive states showed greater improvement with conventional ECT (cortical approach).

Some schizophrenic reactions, particularly chronic conditions, previously resistive to ECT, have in a number of cases shown remarkable improvement with a method combining the cortical and diencephalic approach. This procedure will be described in the following paragraphs.

The technic of non-convulsive diencephalic stimulation, as described in the original report[3] is as follows:

Two specially designed electrodes are used. One is a nasopharyngeal electrode introduced through the nares, reaching the retropharyngeal wall near the body of the sphenoid bone. The other electrode is a scalp electrode placed at the cortex of the skull. It may be used as a double electrode permitting the current to be distributed over a larger area, and to reach lateral areas of the diencephalon. The diencephalon lies in a direct path between the naso-pharyngeal and the scalp electrodes, closer to the small pharyngeal electrode and it is assumed that the density of the electrical field diminishes toward the cortex.

The Reiter RC-47 C or D machines are most suitable for the procedure but older models, such as the CW-47, have been used successfully. In using the newer machines the "ratio" dial is set to 12 o'clock. The current selector is set to #3. Modulation should be about 4 per cecond. The patient has to be anesthetized and for this purpose a 5 percent sodium pentothal solution is injected intravenously within less than a minute, until the patient stops counting. Six to eight cc. of this solution is usually sufficient. Even if respiration should become shallow or stop at the end of the injection, no attention is paid to this fact, but the stimulation is immediately started. The pharyngeal electrode is introduced and the nurse places the scalp electrodes on the skull, about 1 inch R and L of the mid-lines. Current intensities of 1 to 4 milliamps. are then applied for about 30 seconds. During this period the patient displays clonic muscular movements, synchronous with the spikes of the modulated current. After 30 seconds the intensity knob is returned to zero and the patient will immediately breath deeply, even if previous to the current application the respiration might have been inadequate.

After a few respirations the current is again applied and reductions in current intensity are made to avoid cyanosis. The procedure is continued until the patient shows signs of awakening, which in the majority of cases takes three minutes, but occasionally it may have to be extended longer. Upon awakening there is usually marked emotional reaction which may be utilized to elicit dynamic etiologic factors and for supportive psychotherapy.

The first treatments are always given without raising the current above 4 milliamps. but in some disorders, particularly marked hallucinosis, the current intensity has been raised to 15 or 20 milliamps. If this is done mild seizures are observed, but no adverse effects have ever been recorded.

In a number of chronically disturbed patients in which the onset of illness dates back over many years and who did not respond to other therapies, a modification of treatment has been successful in accomplishing at least social improvement. This modification is called "combined cortical and diencephalic treatment"—(C plus D). It seems to replace the electric coma treatment in efficiency but is much simpler and uncomplicated. This combined treatment is started with a conventional GM seizure with ordinary electrodes as in electric coma therapy. As soon as the patient completes the convulsion and be-

gins breathing, a nasopharyngeal electrode is introduced, utilizing the anasthesia following the seizure. (No sodium pentothal is needed.) The convulsive seizure is then followed by 2 to 3 minutes of diencephalic stimulation as described. Good results obtained with this technique in chronic cases include chronic schizophrenics, as well as manic psychoses of long standing and psychotic depressive reactions.

Diencephalic and combined cortical and diencephalic stimulation have been in use for over two years on approximately 270 patients. Evaluation of the therapeutic results is naturally as difficult as evaluation of any psychiatric treatment procedure. However, an attempt to evaluate the effectiveness of the procedure has been made by tabulating patients treated by this method prior to June 1957. The following figures were gathered: Until June 1957, 186 patients received diencephalic stimulation. Of these 91, or 48.92 percent, left the hospital on complete discharge, most of them having been out for over one year without returning.* Sixty more patients, or 32.2 percent, are out on conditional discharge for less than a year. Twelve patients went on conditional discharge but have since returned and are again out on conditional discharge. Nine patients never left the hospital. One figure which is usually recorded in most state hospitals is the total return rate of discharged patients. This varies between 20 and 30 percent. The total return rate of patients treated by this method to date has been 13.2 percent.

Naturally, in the reported group were mostly patients who were considered good candidates. It is by no means assumed that diencephalic stimulation is a cure-all. On the other hand, there are many patients in this group who have been treated previously with ECT, drugs and insulin and did not improve sufficiently to make an extra-mural adjustment.

Thus diencephalic stimulation is considered a valuable adjunct to conventional therapies mainly by reason of its lack of side effects and because it seems to benefit those patients who show the least favorable response to conventional ECT. The reported group of 186 patients included 43 paranoid schizophrenics, of whom 34 or 78 per cent have left the hospital and have not returned. Five have returned for brief periods and 3 never left the hospital. Eight of the total of 43 paranoid schizophrenics have been out for over 2 years, 6 for 1 year.

It is realized that this statistical material is inadequate because of the complexity of the problem and the impossibility of comparing one individual with another, as well as because of the possibility of spontaneous remissions, and the effects of concomitant therapies. However, the results are encouraging and this type of treatment has found a definite place among the therapeutic procedures at the Arizona State Hospital. At the present time, more chronically ill patients are treated in order to evaluate the effectiveness of the treatment in this group of patients. The results of this study will be published at a later date.

Acknowledgment: The development, practice and evaluation of selective electrotherapy has had the continuous interest and support of Dr. Samuel Wick, Director, Arizona State Hospital, whose help and attitude are greatly appreciated.

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*At the time of this printing the figure is 61%.

Phoenix, Arizona.

Multipolar Electrocoma Therapy

(Outline of Three-Lead, Fronto-Bioccipital Stimulation)

EMERICK FRIEDMAN, M.D.

This modality of electrotherapy has been found useful, alone or as an adjunct to standard ECT, in cases displaying phobic anxiety as a prominent part of their symptom complex. It has also been found of value in cases of addiction and alcoholism.

The procedure is no more complicated than any of the other unidirectional techniques but requires brief observation for familiarization by workers experienced in administering ECT with the Reiter apparatus.

Preparation and pre-treatment measures are the same as for ECT. Thiopenthal is given intravenously, usually 10-15 cc. of 5% solution with gr. 1/50 atropine sulfate. Relaxation with succinylcholine (SCC) 10-40 mg. may be obtained if convulsive reactions are anticipated. One electrode is placed on the midfrontal scalp just above the bridge of the nose and one over each mastoid process. An output lead from the apparatus is connected to the frontal electrode and the other lead, consisting of two wires in parallel, connects to the two mastoid electrodes. Thus, from one pole, usually the positive, two parallel wires emerge, or an additional wire with two alligator clips may be used to connect the two mastoid leads if only the standard two-wire outlet cord is available. Electrode paste or solution should be rubbed well into the scalp in order to prevent galvanic cauterization of the skin. (Recently, a saline-detergent emulsion has been found suitable for this purpose.)

The patient is given anesthetic and succinylcholine simultaneously. Electrodes are set and connected, and a mouth gag is applied. The Reiter apparatus is pre-set at *Position #5* (Current Selector Position), *Modulation at 3 o'clock, Ratio at G.M.* (extreme left), (Current Intensity Rheostat), *Amperage at about 5 M.A. on the Sample.* The neck is supported comfortably by a medium-sized pillow, the hands crossed across the chest, the lower extremities supine and uncrossed. The chin is supported firmly by the assistant.

As the *Treat* switch is turned on with one hand, the *Amperage* is increased with the other, very slowly so that full amperage is reached in about 15-20 seconds and held (or) until generalized tonus is reached. During this gradual elevation of amperage the *Polarity Switch* is repeatedly flicked and the *Position* switched down to #1. When tonus is achieved *Amperage* is rapidly decreased to 5-10 ma. for the next 30-40 seconds. *Modulation* is turned to *Full* and *Ratio* to *N.C.* (full to the right). *Polarity* is then switched every 15 seconds. Respiration resumes in less than one minute, usually even with SCC. If not, the *Amperage* is lowered to 1-2 ma. or, if the effects have not been dispelled, positive pressure oxygenation is applied, while the current is still on. When the breathing starts the *Amperage* is slowly raised again to the point where breathing is barely maintained. It will be noted that the expiratory phase of breathing may be forced in a pulsating or rhythmic manner synchronous with generalized myoclonic twitchings. These responses are more prominent when the frontal lead is positive and may be replaced by only facial-neck twitches or fibrillations when the frontal lead is negative. If the myoclonic reaction is not definite enough, the *Position* is reset to #2 or #3. The *Ratio* button may be depressed and released at half-second intervals. The treatment is continued for 3-7 minutes or until signs of consciousness appear, such as purposeful movements of limbs and face, coughing or vocalization. If arousal occurs much before 3 minutes, additional thiopenthal may be given.

In many instances, particularly when agitation and confusion arises in the course of ECT, it has been shown that treatments without the convulsive phenomena are beneficial. The use of this modality of electrostimulation at coma levels may be applied

without convulsive reactions and without myoclonus. The technique for this application is the same as described above, except that the *Amperage* is raised even more slowly than before, the *Position* is pre-set at #3 and the *Ratio* midway between G.M. and S.C. After about a minute of induced tonus the *Position* is moved to #1 and *Ratio* to S.C. *Amperage* is lowered to a point which barely permits respiration. *Modulation* is handled as before. The frontal electrode is kept at *Negative*. If there is evidence of premature wakening, *Amperage* may again be raised to 20 or more ma.

Some precautionary measures should be mentioned. If continued impairment of respiration occurs even with low amperage the chin should be more firmly supported, keeping the neck well extended; tugging at the protruding part of the mouth gag usually accomplishes this. If respiration is still irregular, the mastoid electrodes should be moved superiorly an inch or so. Asymmetric placement of electrodes is to be avoided. The frontal electrode should be exactly in the mid-line and the mastoid electrodes carefully, symmetrically placed. Otherwise, a marked lateral tonus and myoclonus may result, together with disturbing random movements and restlessness.

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Albany, N. Y.

Electro-Sleep in a Chronic Disturbed Service

MAURICE FENICHEL, M.D.

At this time I should like to discuss and attempt clarification of some of the varied opinions with respect to the safest way for administering electro-sleep treatment. The points of interest may be outlined as follows:

1. Role of electro-sleep.
2. Duration and intensity of treatment.
3. Advantages and disadvantages of electro-sleep, side effects and complications.
4. Problems connected with Anectine and Pentothal.
5. The problem of stimulation.
6. Something about the newer techniques and indications.
7. Electro sleep and tranquilizers.
8. Electro sleep and psychotherapy.
9. Results and failures.

A patient in the first year of treatment for his mental disorder is routinely given special therapies such as electroshock, insulin, tranquilizers, or combinations of these. If they prove inadequate, electro-sleep treatment is tried. Electro-sleep tends to relieve extensive anxiety in psychotics with weakened ego, thus avoiding a progressive break with reality and deterioration in the patients' faulty defense mechanisms. Intensive electro-sleep treatment helps provide the basis for mental reintegration, progressively improved stability, better contact with reality, and availability for rehabilitation through intensive activity programs and psychotherapy.

Duration and Intensity of Treatment: To date our treatment procedure has been carried out with two treatments a week. In view of relapse which sometimes have occurred, I tend to follow the regimen of Drs. Bogen-Tietz & Jordan who recommend daily electro-narcosis during the first week, followed by two treatments the second week and maintenance treatment once a week thereafter, or even at wider spacing of time until insight is obtained. I feel that this integrated phase should be attained as soon as possible, and that active intensive treatment of high order is justified, so that the acute patient may receive as early as possible benefit before the psychotic manifestations increase to a severe stage.

Why electro-sleep rather than regular electroshock? Because electro-sleep is safer, freer of side effects such as respiratory and cardiovascular difficulties, dislocations, and fractures and because electro-stimulation is an additional beneficial factor it can be applied with deep effect in even severe cardiacs, in cases of auricular fibrillations, aneurysms, as well as severe epileptic cases. Even in severe melancholia, deep depression, or stupor where a convulsive treat-

ment would normally be indicated, it is now my opinion that prolonged stimulation with the Reiter Electrostimulator is more effective than convulsive treatment alone.

The use of succinylcholine (SCC) and thiopenthal (Pentothal) has been recommended in the past. Lately I have used SCC with all treatments involving grand mal in approximately 5,000 treatments over a period of 5 years. I did not have a single fatality. Statistics for New York State record an average of one death per 1,000 patients receiving electroshock therapy, and possibly in every 500 cases one dislocation or fracture involving usually the vertebra or ribs and without serious complications. Despite the obvious advantage of SCC in elimination of muscular violence, possible prevention of brain hemorrhages, ruptures of aneurysms, etc., it now appears that the number of fatalities is increasing when ECT is given with SCC. This increase may be attributed to the large doses given which delay return of breathing in spite of oxygen administration and cause bradycardias and tachycardias or respiratory or cardiac arrest.

We have uncovered a further problem in connection with the use of SCC in electro-sleep treatment, namely, that the SCC reduces considerably the ability of the patient to tolerate the electro-sleep treatment. As a result, we have been compelled to give shorter treatments in those cases where we used SCC. Furthermore, cases of fatality after SCC administration with only 15 or 20 milligrams have been described, death occurring even before electric shock could be given. Since these anaphylatic reactions might occur during subsequent treatments which cannot be predetermined, we have usually started our treatments with only 5 milligrams SCC and gradually increased the dosage occasionally to a maximum of 12 milligrams administered intravenously. If side reactions such as breathing difficulties, cyanosis, bradycardia, or acute drop in blood pressure occur, I terminate treatment at once and continue to give effective stimulation on the upper fronto temporal areas for at least ten to 20 minutes. The patient usually recovers easily.

Many use thiopenthal and SCC together routinely. I have found that the patient's fears of and antagonisms to treatment are definitely reduced when thiopenthal is given. We usually give frightened patients three or more grains (180 mg.) amobarbital (Amytal) orally two hours prior to treatment. Although I never observed difficulties in connection with thiopenthal, it is possible that it counteracts the effect of SCC, and may cause breathing difficulty, and also may cause cardiovascular disturbance. On the basis of clinical experience and from the standpoint of safety I would prefer to use mild electro-stimulation, rather than deep electro-sleep with SCC.

Our principal concern has been to find ways of making the electro-sleep treatment thoroughly safe. We know that cases of over-sensitivity to thiopenthal have occurred time and again, not only in psychiatric cases, but also in operating rooms. The same is true with respect to SCC. We therefore prefer to minimize the dose of these drugs in connection with the electro-sleep treatment. Moreover, we shift the site of the electrodes during the electro-sleep treatment in order not to over stimulate any one area of the brain and to treat the entire brain as effectively as possible. We try to adjust the treatment in each case to fit the individual patient. Where we have overstimulated with a resulting bradycardia, extra systoles, or respiratory difficulties, we have terminated the active treatment and continued stimulation to the brain in the bi-fronto temporal areas for as long as 20 minutes until the awareness of the patient returned and he showed signs of distinct motor activity. However, frightened patients are best treated with preliminary injections of thiopenthal. In all cases we prefer to have a preliminary thorough physical checkup, and not to rely on the routine electro-cardiogram alone. We also like to minimize the intensity of the electrical simulation to meet the patient's actual needs. If we exceed this necessary amount, we are more likely to attain electro-irritation of the brain, hyperstimulation of vital centers like the vagus, which might cause cardiac arrest.

Since our main goal is good and lasting therapeutic results, it is important that electro-sleep treatment be given intensively, and also that it be followed by intensive psycho-

therapy whenever possible. Psychotherapy may actually be considered an integral part of electro-sleep treatment. Good contact with environment aids the patient to attain confidence and insight into his condition thus strengthening his ego and prevents faulty defense mechanisms. It is conceivable that chlorpromazine may be useful on a maintenance basis after the patient has left the hospital.

In addition to the bifrontal and monopolar electrode placements described in a previous paper, we have had occasion to use the endonasal method presented by Breitner. Although he uses Position 3 current for this purpose, I have found the treatment smoother with the milder Position 5 current for deep treatment so that I can use more current with less side effects.

We give grand mal electro-sleep where there is under activity, stupor, depression, melancholia, or withdrawal. In general we initiate the treatment with a bi-polar grand mal, and continue with the monopolar stimulation at current selector Position 5. We initiate treatment with stimulation for one minute at about six or seven milliamps (ma) and then reduce to two or three ma. This technique has the advantage that we can treat safely with lower currents for longer periods of time.

We employ thiopenthal monopolar electro-sleep in cases that are over active, greatly disturbed, tense, anxious, in catatonic or other schizophrenic excitements with violent tendencies.

The endonasal method, usually used with thiopenthal and non-convulsive stimulation, often results in abreaction, so that the patient awakes with crying or laughing spells. This treatment is suggested where serious emotional disturbances occur and our paranoid schizophrenics have shown great improvement.

Tranquilizers should not be combined with electro-sleep treatment simultaneously. The additional hazard involved has already been pointed out, and we would like to reiterate those cautions. However, we feel that tranquilizers may be used with benefit following electro-sleep treatment.

Electro-sleep should definitely be tried before embarking on psychosurgery. It is a very intensive treatment and fulfills the need required in "push therapy," to obtain better personality reorganization. However, there is no doubt that there will be cases where psychosurgery is the ultimate resort.

Our results have been followed closely in 90 cases where treatment has been completed; 49% may be classed improved under the category of very good, good, or fair. These were treated by the grand mal bipolar technique followed by monopolar stimulation, or they were treated with thiopenthal monopolar method according to the indications mentioned above. In 51% of the cases we had no appreciable results. When we used Breitner's endonasal method, we achieved 54% good to fair results and 46% with no results. All of these patients were "hard core" cases. We have released 13 patients from the hospital on convalescent care, and of these only one was returned after a few months and he is now receiving a second course of treatment.

It is our observation that patients suffering from severe mental disorders, who have not reacted to any other type of chemical or physical treatment, the so-called "hard core" cases, have shown good improvement with electro-sleep in a significant number of cases.

Kings Park, New York

Abreaction Produced by Low Non-Convulsive Electrostimulation

PAUL H. WILCOX, M.D.
Traverse City, Michigan

10-11-57

CASE A. F. Male, single, aged 29.

1957 Wilcox Psychiatric Rating Scale

Rating Scale	Significant Scores	ECT Analysis Scores
Depression	4+	1
Retardation	3+	1
Agitation	1+	0
Sleeplessness	2+	1
Depersonalization	3+	0
Unreality	0	1
Ideas of reference	1+	0
Delusions of persecution	0	1
Memory	0	1
Anxiety	4+	–
Invisible presence	3+	–

Interpretation

Although depression was a prominent symptom with 3 out of 4 indications for ECT, the presence of 3+ depersonalization, 1+ ideas of reference, 4+ anxiety and 3+ feelings of an invisible presence indicated that the depression is probably predominantly reactive in type. Therefore the therapeutic decision was to try the patient on low non-convulsive electrostimulation as first choice.

Demonstration

The patient was given I.V. Sodium Pentothal slowly according to the Impastato technique, optimum anesthesia level being obtained with 0.5 gm. Then the patient was stimulated with the Reiter Electrostimulator RC47D using Current #5. The electrodes were applied in the biparieto-mastoid region. The following current-time factors were given:

ma.	*min.*
10	0.05
5	0.35
3	0.60
0.5	0.20

The stimulation was discontinued at the end of 1.20 min. when the patient first swallowed. Respirations had been suppressed for the first 0.60 min. and then came through nicely. Color was good at all times.

After stimulation was terminated the patient lay quietly for 2 min. and then spoke spontaneously in a groggy tone. Provocative psychotherapy was begun in order to elicit an emotional abreaction by having him repeat one to three times such phrases as, "I don't know what to do with my poor little self," "I don't really know what breaks my heart," "I unconsciously feel doomed to be a miserable wretch," "I don't know why I'm afraid," etc. He began to react emotionally and blurted out something about this goddamn place. He was then instructed to say, "I don't know what to do in this goddamn place," and then was urged to repeat it louder and louder. After the third and loudest repetition, he broke out into loud wailing moans. These were fostered by further phrases—suhc as, "I'm nursing a grudge phrases—such as, "I'm nursing a grudge against God." He wailed that he did not know if there was a God. Then I had him say, "I don't know what to do without a God." This further increased his sobbing and wailing. Then he volunteered that he felt good getting all this attention and getting all these feelings out. He was interviewed later and apologized for making a scene but said it had been a relief to get those feelings out.

Discussion

This demonstration vindicated the therapeutic decision to give non-convulsive electrostimulation rather than ECT because the depressive feelings were expressed with a subsequent feeling of relief. The ESnc decreased his emotional resistance but aggressive psychotherapy was necessary in order to bring out the abreaction satisfactorily.

CONSTITUTION (Revised)

EASTERN PSYCHIATRIC RESEARCH ASSOCIATION, INC.

Article: I: NAME

This Association shall be called EASTERN PSYCHIATRIC RESEARCH ASSOCIATION, INC.

Article II: OBJECT

The object of this Society is to further the standards of psychiatric practice and knowledge.

Article III: MEMBERS

The number of members and associate members is not limited.

Members shall not be barred for reasons of race, color, creed or sex.

There shall be three classes of members:

1. *Active Members:* Active members shall be physicians of good ethical standing, having specialized in the practice of psychiatry for at least three years and whose qualifications have been verified by and are acceptable to the Membership Committee. Active members only shall be eligible to office and entitled to vote.

2. *Associate Members:* Associate members shall be physicians in good ethical standing and in process of training and whose qualifications are verified by and acceptable to the Membership Committee.

3. *Advisory Members:* Advisory members shall be physicians or doctors of philosophy working in the biochemical or allied fields with particular interest in psychiatric research.

Article IV: OFFICERS

The officers of the Society shall be a President, President-Elect, 1st Vice-President, 2nd Vice-President, Secretary-Treasurer, and Assistant Secretary-Treasurer and an Executive Committee of six members. These officers and members of the Executive Committee are to be elected by the Society as follows: Six in groups of two each year and the officers shall be ex-officio members of the Executive Committee.

Article V: DUTIES & POWERS OF OFFICERS

The President is the chief executive officer of the Society. He shall preside at all meetings of the Society, appoint the chairman and members for the necessary committees and shall in general perform such duties as are customary for presiding officers.

The President-Elect automatically becomes President at the end of the term of the incumbent President.

The 1st Vice-President is charged with the duties of the President in his absence and of presiding at the meeting of the Executive Committee.

The 2nd Vice-President assists and takes the place of the 1st Vice-President in any or all of his duties when necessary.

The Secretary-Treasurer shall keep a record of the proceedings of all meetings of the Society and of the Executive Committee; certify official records; procure and sign, with the president, certificates of membership; keep a list of the members and associate members; issue notices of all meetings and have charge of all funds and shall have the power to collect dues. He shall pay all expenses by and with the consent and approval of the Executive Committee.

The Assistant Secretary-Treasurer assists the Secretary-Treasurer.

The Executive Committee shall have charge of all business of the Society between meetings and its action may be over-ruled at meetings of the Society.

At the annual meeting which takes place at a time to be fixed in the By-Laws, the President, Secretary-Treasurer and the Executive Committee shall each present a report of official transactions during the past year.

The Executive Committee shall act as a Nominating Committee.

Article VI: ELECTION OF OFFICERS

Officers shall be nominated at the April meeting and elected at the following meeting and shall hold office for one year, commencing in October. The President shall be eligible for reelection, but for not more than two consecutive terms of office.

Article VII: MEETINGS

Meetings shall be either stated or special, as defined in the By-Laws.

Article VIII: AMENDMENTS

Proposed amendments to the Constitution shall be made in writing at a stated meeting and referred to the Executive Committee for consideration which shall report them at two consecutive meetings. Thereafter proposed amendments to become effective must be endorsed by a two-thirds mail vote which shall represent at least twenty-five per cent (25%) of the membership.

CONSTITUTION BY-LAWS

Article I: MEETINGS

1. The regular meetings of the Society shall be held on the first Friday of February, April, June and December. If any such Friday falls on a legal holiday, the meeting for that month shall take place on the preceding Friday. The annual meeting shall be held in October.

2. Special meetings may be called by the Executive Committee.

3. Regular meetings shall begin at 8:30 P.M. and special meetings at the hour designated by the Executive Committee.

4. Ten per cent (10%) of active members, or ten members, whichever is the larger, shall constitute a quorum for purposes of a business meeting.

5. Four members of the Executive Committee shall constitute a quorum for that Committee.

6. The Executive Committee shall meet at the call of the Vice-President or two members of the Executive Committee.

Article II: ADMISSION OF MEMBERS

1. The names of applicants for membership shall be presented to the secretary in writing on a printed form provided for such purpose and endorsed by two active members of the Society. The secretary shall present applications for membership to the Membership Committee. Candidates whose applications have been processed shall have their names presented at the next regular, or some subsequent meeting, their names having been printed in the notice of such meeting. A majority of votes cast at the designated meeting shall be necessary for election to the Society.

2. Every active and associate member shall sign the Constitution within three months after his election, failing which, said election shall be deemed void unless a satisfactory excuse is given.

3. Associate members who present evidence of compliance with the requirements for active membership shall be admitted to that category. All associate members must fulfill this requirement for active membership within a period of five years after date of acceptance in this Society or otherwise be stricken from the Society's rolls.

Article III: DUES

1. The annual dues for active and special research members shall be Fifteen dollars ($15.00) and for Associate members, Ten dollars ($10.00).

2. All persons elected for active membership, after having complied with the requirements of the Constitution and By-Laws, shall be issued a certificate of active membership, authenticated by the signature of the President or Vice-President, and Secretary-Treasurer, with the Seal of the Society affixed.

3. Any member who shall fail for one year to pay his dues, may, after twenty days' notification by registered mail from the Treasurer, have his name stricken from the list of members by the Executive Committee. The payment of dues may be waived by the Executive Committee for good and sufficient reason.

4. The fiscal year of the Society shall be co-extensive with the calendar year.

Article IV: REGISTRATION AND DISMISSAL

Any member may resign by signifying his intention to do so to the Secretary-Treasurer in writing.

Charges against a member or officer, except for non-payment of dues, as before provided, shall be made in writing to the Executive Committee, which, after a hearing of the accused on notification to attend, and due examination into such charges, may acquit, admonish, suspend, or expel a member as it thinks proper. In the case of an officer, they shall report to the Society for its action. Members under charge may have counsel at the hearings of the Executive Committee. The right of appeal from action of the Committee to the membership-at-large may not be denied.

Article V: NOMINATION AND ELECTION OF OFFICERS AND MEMBERS OF THE EXECUTIVE COMMITTEE

1. The President shall appoint a Nominating Committee in October of each year. This Committee shall be endorsed by the Executive Committee. Nomination of officers shall be made by the Nominating Committee at the meeting in April or at the annual meeting, and election shall be by vote at the next regular meeting. Additional nominations may be made from the floor.

2. The Secretary-Treasurer shall cause the names of the nominee for each office to be printed on cards, a copy of which shall be sent to each member with the notice of election.

3. Vacancies in office may be filled at any time by nomination at one meeting and election as in Section 1 of this Article.

Article VI: ORDER OF BUSINESS

At all regular meetings the following shall be the order of business:

1. Presentation of clinical material. Exhibition of normal or pathological speciments, apparatus, etc.

2. Papers of the evening.

All business not of scientific nature shall be transacted in Executive Session at the close of the regular scientific program under the following order:

1. Reading of the minutes of the previous meeting.
2. Reports of Standing Committees:
   a. Executive.
   b. Membership.
3. Reports of Special Committees.
4. Election of proposed members.
5. Unfinished business.
6. Nomination of officers.

The order of business may be altered at the discretion of the President. These By-Laws may be suspended or amended. Two-thirds of all votes cast at a regular meeting shall be sufficient to suspend them. For their amendment, the same rule and same vote shall be required as for amendments of the Constitution. (See Article VIII of the Constitution.)

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